

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
4 March 2004 (04.03.2004)

PCT

(10) International Publication Number  
**WO 2004/017912 A2**

- (51) International Patent Classification<sup>7</sup>: **A61K** **BURCH, Jarrett; 2841 Stuart Drive, Durham, NC 27707 (US).**
- (21) International Application Number: **PCT/US2003/026366** (74) Agent: **MACBLAIN, Thomas, D.; Gallagher & Kennedy, P.A., 2575 East Camelback Road, Phoenix, AZ 85016-9225 (US).**
- (22) International Filing Date: **22 August 2003 (22.08.2003)**
- (25) Filing Language: **English** (81) Designated States (*national*): **AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.**
- (26) Publication Language: **English**
- (30) Priority Data:  
60/405,199 22 August 2002 (22.08.2002) **US**  
60/448,953 21 February 2003 (21.02.2003) **US**
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- (84) Designated States (*regional*): **ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).**
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- Published:**  
— *without international search report and to be republished upon receipt of that report*
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

WO 2004/017912 A2

(54) Title: **METHODS FOR INCREASING THE RATE OF HEART MUSCLE CONTRACTION**

(57) Abstract: The present invention provides methods for increasing the contractile rate in heart muscle and methods for treating of preventing various heart muscle disorders, by administering to an individual in need thereof one or more of the heat shock protein 20-derived peptides disclosed herein.

## METHODS FOR INCREASING THE RATE OF HEART MUSCLE CONTRACTION

### Cross Reference

This application claims priority to U.S. Provisional Patent Application Serial  
5 Nos. 60/405,199 filed August 22, 2002 and 60/448,953 filed February 21, 2003, both  
of which are incorporated by reference herein in their entirety.

### Field of Invention

This invention relates generally to methods for increasing the contractile rate  
in heart muscle and methods for treating and preventing cardiac disorders.

### 10 Background of the Invention

Several recent studies have demonstrated that nitric oxide has direct effects on  
myocardial contractile function. Exogenous nitric oxide donors characteristically  
enhance relaxation without major effects on peak systolic function. This selective  
relaxant action has been observed in papillary muscle preparations, intact hearts, and  
15 cardiac myocytes.

It has recently been determined that cyclic nucleotide-dependent relaxation of  
vascular smooth muscle is associated with an increase in the phosphorylation of the  
small heat shock related protein 20 ("HSP20"), and peptides derived from HSP20.  
HSP20 is highly and constitutively expressed in muscle tissues and can be  
20 phosphorylated in vitro by cGMP-dependent protein kinase.

However, the role of HSP20 and peptides derived therefrom in modulation of  
the contractile response in cardiac muscles is not known. Increasing the contractile  
rate in heart muscle would be of value in the prevention and treatment of various  
cardiac disorders.

### 25 Summary of the Invention

The present invention provides methods for increasing the contractile rate in  
heart muscle comprising administering to an individual in need thereof an amount  
effective to increase the contractile rate in heart muscle of one or more polypeptides  
comprising a sequence disclosed herein. In a preferred embodiment, increasing the  
30 contractile rate in heart muscle comprises increasing the rate of heart muscle

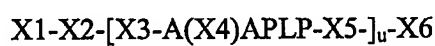
relaxation. In a further preferred embodiment, the individual to be treated suffers from one or more of bradyarrhythmia, bradycardia, congestive heart failure, stunned myocardium, pulmonary hypertension, and diastolic dysfunction.

In another aspect, the present invention comprises methods for treating or preventing a cardiac disorder comprising administering to an individual suffering from one or more of bradyarrhythmia, bradycardia, congestive heart failure, stunned myocardium, pulmonary hypertension, and diastolic dysfunction an amount effective to increase heart muscle contraction rate of one or more polypeptides comprising a sequence disclosed herein.

## 10 Detailed Description of the Invention

In one aspect, the present invention provides methods for increasing the contractile rate in heart muscle comprising administering to an individual in need thereof an amount effective to increase the contractile rate in heart muscle of one or more polypeptides comprising a sequence according one or more of:

15 (a) general formula I:



wherein X1 is absent or is one or more molecules comprising one or more aromatic ring;

X2 is absent or comprises a transduction domain;

20 X3 is 0, 1, 2, 3, or 4 amino acids of the sequence WLRR (SEQ ID NO:1);

X4 is selected from the group consisting of S, T, Y, D, E, hydroxylysine, hydroxyproline, phosphoserine analogs and phosphotyrosine analogs;

X5 is 0, 1, 2, or 3 amino acids of a sequence of genus Z1-Z2-Z3,

wherein Z1 is selected from the group consisting of G and D;

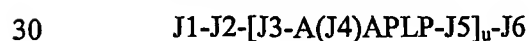
25 Z2 is selected from the group consisting of L and K; and

Z3 is selected from the group consisting of S, T, and K;

X6 is absent or comprises a transduction domain; and

wherein u is 1-5; and

(b) general formula II:-



wherein J1 is absent or is one or more molecules comprising one or more aromatic ring;

J2 is absent or comprises a cell transduction domain;

J3 is 0-14 amino acids of the sequence of heat shock protein 20 between residues 1 and 14 of **SEQ ID NO: 298**;

J4 is selected from the group consisting of S, T, Y, D, E, hydroxylysine, 5 hydroxyproline, phosphoserine analogs and phosphotyrosine analogs;

J5 is 0-140 amino acids of heat shock protein 20 between residues 21 and 160 of **SEQ ID NO:298**; and

J6 is absent or comprises a cell transduction domain.

As used herein, an "individual in need thereof" means an individual that can 10 benefit from an increased heart muscle contractile rate. Such individuals are those who exhibit a reduced heart rate relative to either a normal heart rate for the individual, or relative to a "normal" heart rate for a similarly situated individual.

As used herein, the phrase "increasing the contractile rate in heart muscle" means any increase in contractile rate that provides a therapeutic benefit to the patient. 15 Such a therapeutic benefit can be achieved, for example, by increasing the contractile rate to make it closer to a normal contractile rate for the individual, a normal contractile rate for a similarly situated individual, or some other desired target contractile rate.

In a preferred embodiment, the methods of the invention result in an increase 20 of at least 5% in the contractile rate of the patient in need of such treatment. In further preferred embodiments, the methods of the invention result in an increase of at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, and/or 50% in the contractile rate of the patient in need of such treatment.

In a preferred embodiment, increasing the contractile rate in heart muscle is 25 accomplished by increasing the heart muscle relaxation rate (ie: if the muscles relax faster they beat faster). In a more preferred embodiment, the methods of the invention result in an increase of at least 5% in the heart muscle relaxation rate of the patient in need of such treatment. In further preferred embodiments, the methods of the invention result in an increase of at least 10%, 15%, 20%, 25%, 30%, 35%, 40%, 30 45%, and/or 50% in the heart muscle relaxation rate of the patient in need of such treatment.

In a preferred embodiment of this aspect of the invention, the methods are performed to treat one or more heart cardiac disorders that can benefit from increasing the contractile rate in heart muscle. Such cardiac disorders include bradyarrhythmias,



bradycardias congestive heart failure, pulmonary hypertension, stunned myocardium, and diastolic dysfunction.

As used herein, "bradyarrhythmia" means an abnormal decrease of the rate of the heartbeat to less than 60 beats per minute, generally caused by a disturbance in the electrical impulses to the heart. A common cause of bradyarrhythmias is coronary heart disease, which leads to the formation of atheromas that limit the flow of blood to the cardiac tissue, and thus the cardiac tissue becomes damaged. Bradyarrhythmias due to coronary artery disease occur more frequently after myocardial infarction. Symptoms include, but are not limited to, loss of energy, weakness, syncope, and hypotension.

As used herein, "Congestive heart failure" means an inability of the heart to pump adequate supplies of blood throughout the body. Such heart failure can be due to a variety of conditions or disorders, including but not limited to hypertension, anemia, hyperthyroidism, heart valve defects including but not limited to aortic stenosis, aortic insufficiency, and tricuspid insufficiency; congenital heart defects including but not limited to coarctation of the aorta, septal defects, pulmonary stenosis, and tetralogy of Fallot; arrhythmias, myocardial infarction, cardiomyopathy, pulmonary hypertension, and lung disease including but not limited to chronic bronchitis and emphysema. Symptoms of congestive heart failure include, but are not limited to, fatigue, breathing difficulty, pulmonary edema, and swelling of the ankles and legs.

As used herein, "Stunned myocardium" means heart muscle that is not functioning (pumping/beating) due to cardiac ischemia (lack of blood flow/oxygen to the vessels supplying the heart muscle).

As used herein, "Diastolic dysfunction" means an inability of the heart to fill with blood during diastole (the resting phase of heart contraction). This condition usually occurs in the setting of left ventricular hypertrophy. The heart muscle becomes enlarged and stiff such that it cannot fill adequately. Diastolic dysfunction can result in heart failure and inadequate heart function.

As used herein, "Pulmonary hypertension" means a disorder in which the blood pressure in the arteries supplying the lungs is abnormally high. Causes include, but are not limited to, inadequate supply of oxygen to the lungs, such as in chronic bronchitis and emphysema; pulmonary embolism, and intestinal pulmonary fibrosis. Symptoms and signs of pulmonary hypertension are often subtle and nonspecific. In

the later stages, pulmonary hypertension leads to right heart failure that is associated with liver enlargement, enlargement of veins in the neck and generalized edema.

In a further aspect, the present invention provides methods for treating a heart muscle disorder comprising administering to an individual suffering from one or more  
5 of bradyarrhythmia, bradycardia, congestive heart failure, stunned myocardium, pulmonary hypertension, and diastolic dysfunction an amount effective to increase heart muscle contractile rate of one or more polypeptides comprising or consisting of a sequence according to one or more of general formulas I and II.

As used herein, "treat" or "treating" means accomplishing one or more of the  
10 following: (a) reducing the severity of the disorder; (b) limiting or preventing development of symptoms characteristic of the disorder(s) being treated; (c) inhibiting worsening of symptoms characteristic of the disorder(s) being treated; (d) limiting or preventing recurrence of the disorder(s) in patients that have previously had the disorder(s); and (e) limiting or preventing recurrence of symptoms in patients that  
15 were previously symptomatic for the disorder(s).

For example, treating bradyarrhythmia includes one or more of the following  
(a) improving the rate of the heartbeat to closer to normal levels for the individual, closer to a desired rate, or increasing to at least above 60 beats per minute; (b)  
20 preventing the occurrence of one or more of loss of energy, weakness, syncope, and hypotension in patients suffering from bradyarrhythmia; (c) inhibiting worsening of one or more of loss of energy, weakness, syncope, and hypotension in patients suffering from bradyarrhythmia and its symptoms; (d) limiting or preventing recurrence of bradyarrhythmia in patients that previously suffered from bradyarrhythmia; and (e) limiting or preventing recurrence of one or more of loss of  
25 energy, weakness, syncope, and hypotension in patients that previously suffered from bradyarrhythmia.

Similarly, treating congestive heart failure includes one or more of the following (a) improving the heart's ability to pump adequate supplies of blood throughout the body to closer to normal levels for the individual, or closer to a desired  
30 pumping capacity; (b) limiting or preventing development of one or more of fatigue, breathing difficulty, pulmonary edema, and swelling of the ankles and legs in patients suffering from congestive heart failure; (c) inhibiting worsening of one or more of fatigue, breathing difficulty, pulmonary edema, and swelling of the ankles and legs in patients suffering from congestive heart failure and its symptoms; (d) limiting or

preventing recurrence of congestive heart failure in patients that previously suffered from congestive heart failure; and (e) limiting or preventing recurrence of one or more of fatigue, breathing difficulty, pulmonary edema, and swelling of the ankles and legs in patients that previously suffered from congestive heart failure.

5 Treating stunned myocardium means one or more of (a) improving the ability of the heart muscle to pump by improving the oxygenation of the ischemic muscle, or by decreasing the need of the myocardial cells for oxygen and (b) limiting or preventing recurrence of stunned myocardium in patients that previously suffered from stunned myocardium.

10 Similarly, treating diastolic dysfunction includes one or more of (a) limiting or preventing heart failure and/or inadequate heart function by allowing the heart to relax and fill more completely; (b) limiting or preventing recurrence of diastolic dysfunction in patients that previously suffered from diastolic dysfunction; and (c) limiting or preventing recurrence of heart failure and/or inadequate heart function in  
15 patients that previously suffered from diastolic dysfunction.

Treating pulmonary hypertension includes one or more of the following (a) decreasing blood pressure in the arteries supplying the lungs to closer to normal levels for the individual, or closer to a desired pressure; (b) limiting or preventing the occurrence of one or more of enlargement of veins in the neck, enlargement of the  
20 liver, and generalized edema in patients suffering from pulmonary hypertension; (c) inhibiting worsening of one or more of enlargement of veins in the neck, enlargement of the liver, and generalized edema in patients suffering from pulmonary hypertension and its symptoms; (d) limiting or preventing recurrence of pulmonary hypertension in patients that previously suffered from pulmonary hypertension; and (e) limiting or  
25 preventing recurrence of one or more of enlargement of veins in the neck, enlargement of the liver, and generalized edema in patients that previously suffered from pulmonary hypertension.

In a further aspect, the present invention provides methods for preventing a heart muscle disorder comprising administering to an individual at risk of developing  
30 bradyarrhythmia, bradycardia, congestive heart failure, stunned myocardium, pulmonary hypertension, and diastolic dysfunction an amount effective to increase heart muscle contractile rate of one or more polypeptides comprising or consisting of a sequence according to one or more of general formulas I and II.

As used herein, the term "prevent" or "preventing" means to limit the disorder in individuals at risk of developing the disorder.

For example, methods to prevent congestive heart failure involve administration of the polypeptides as described above to a subject that suffers from one or more of hypertension, anemia, hyperthyroidism, heart valve defects including but not limited to aortic stenosis, aortic insufficiency, and tricuspid insufficiency; congenital heart defects including but not limited to coarctation of the aorta, septal defects, pulmonary stenosis, and tetralogy of Fallot; arrhythmias, myocardial infarction, cardiomyopathy, pulmonary hypertension, and lung disease including but not limited to chronic bronchitis and emphysema.

Similarly, methods to prevent bradyarrhythmia involve administration of the polypeptides as described above to a subject that suffer from one or more of coronary heart disease and atheroma formation, or that previously had a myocardial infarction or conduction disorder.

Similarly, methods to prevent pulmonary hypertension involve administration of the polypeptides as described above to a subject that suffers from one or more of chronic bronchitis, emphysema, pulmonary embolism, and intestinal pulmonary fibrosis.

Preventing stunned myocardium involves administration of the polypeptides as described above to a subject that suffers from cardiac ischemia.

Preventing, treating diastolic dysfunction involves administration of the polypeptides as described above to a subject that suffers from left ventricular hypertrophy

As used herein, an "amount effective" of the one or more polypeptides is an amount that is sufficient to provide the intended benefit of treatment. An effective amount of the polypeptides that can be employed ranges generally between about 0.01  $\mu\text{g/kg}$  body weight and about 10  $\text{mg/kg}$  body weight, preferably ranging between about 0.05  $\mu\text{g/kg}$  and about 5  $\text{mg/kg}$  body weight.

The term "polypeptide" is used in its broadest sense to refer to a sequence of subunit amino acids, amino acid analogs, or peptidomimetics. The subunits are linked by peptide bonds, except where noted (including when the X2 position is a non-amino acid molecule that contains an aromatic ring). The polypeptides described herein may be chemically synthesized or recombinantly expressed. Recombinant expression can be accomplished using standard methods in the art, generally involving the cloning of

nucleic acid sequences capable of directing the expression of the polypeptides into an expression vector, which can be used to transfect or transduce a host cell in order to provide the cellular machinery to carry out expression of the polypeptides. Such expression vectors can comprise bacterial or viral expression vectors, and such host  
5 cells can be prokaryotic or eukaryotic.

Preferably, the polypeptides for use in the methods of the present invention are chemically synthesized. Synthetic polypeptides, prepared using the well-known techniques of solid phase, liquid phase, or peptide condensation techniques, or any combination thereof, can include natural and unnatural amino acids. Amino acids  
10 used for peptide synthesis may be standard Boc (N $\alpha$ -amino protected N $\alpha$ -t-butyloxycarbonyl) amino acid resin with the standard deprotecting, neutralization, coupling and wash protocols of the original solid phase procedure of Merrifield (13), or the base-labile N $\alpha$ -amino protected 9-fluorenylmethoxycarbonyl (Fmoc) amino acids first described by Carpino and Han (5). Both Fmoc and Boc N $\alpha$ -amino protected  
15 amino acids can be obtained from Sigma, Cambridge Research Biochemical, or other chemical companies familiar to those skilled in the art. In addition, the polypeptides can be synthesized with other N $\alpha$ -protecting groups that are familiar to those skilled in this art.

Solid phase peptide synthesis may be accomplished by techniques familiar to  
20 those in the art and provided, for example, in (17, 7) or using automated synthesizers. The polypeptides of the invention may comprise D-amino acids (which are resistant to L-amino acid-specific proteases in vivo), a combination of D- and L-amino acids, and various "designer" amino acids (e.g.,  $\beta$ -methyl amino acids, C $\alpha$ -methyl amino acids, and N $\alpha$ -methyl amino acids, etc.) to convey special properties. Synthetic amino acids  
25 include ornithine for lysine, and norleucine for leucine or isoleucine.

In addition, the polypeptides can have peptidomimetic bonds, such as ester bonds, to prepare polypeptides with novel properties. For example, a peptide may be generated that incorporates a reduced peptide bond, i.e., R<sub>1</sub>-CH<sub>2</sub>-NH-R<sub>2</sub>, where R<sub>1</sub> and R<sub>2</sub> are amino acid residues or sequences. A reduced peptide bond may be  
30 introduced as a dipeptide subunit. Such a polypeptide would be resistant to protease activity, and would possess an extended half-life in vivo.

In a preferred embodiment of the polypeptides according to general formula I for use in the methods, X<sub>4</sub> is phosphorylated. In a further preferred embodiment of

the polypeptides according to general formula I, at least one of X2 and X6 comprises a transduction domain.

According to various embodiments of the polypeptides of general formula I, the region [X3-A(X4)APLP-X5]<sub>n</sub> may be present in 1, 2, 3, 4, or 5 copies. In a preferred embodiment, it is present in 1 copy. In other embodiments, it is present in multiple copies to provide increased efficacy for use in the methods of the invention.

According to various embodiments of the polypeptides of general formula I, X4 is S, T, Y, D E, a phosphoserine mimic, or a phosphotyrosine mimic. It is more preferred that X4 is S, T, or Y; more preferred that X4 is S or T, and most preferred that X4 is S. In these embodiments where X4 is S, T, or Y, it is most preferred that X4 is phosphorylated. When X4 is D or E, these residues have a negative charge that mimics the phosphorylated state. The polypeptides of general formula I are optimally effective in the methods of the invention when X4 is phosphorylated, is a phosphoserine or phosphotyrosine mimic, or is another mimic of a phosphorylated amino acid residue, such as a D or E residue. Examples of phosphoserine mimics include, but are not limited to, sulfoserine, amino acid mimics containing a methylene substitution for the phosphate oxygen, 4-phosphono(difluoromethyl)phenylalanine, and L-2-amino-4-(phosphono)-4,4-difluorobutanoic acid. Other phosphoserine mimics can be made by those of skill in the art; for example, see (15). Examples of phosphotyrosine mimics include, but are not limited to, phosphonomethylphenylalanine, difluorophosphonomethylphenylalanine, fluoro-O-malonyltyrosine and O-malonyltyrosine. (See, for example, (1)).

In another embodiment of the polypeptides of general formula I, X1 is one or more molecules comprising an aromatic ring. In one preferred embodiment, the one or molecules comprising an aromatic ring are amino acids, and X1 is (F/Y/W)<sub>z</sub>, wherein "z" is 1-5 amino acids. Thus, for example, X1 can be 1 or 2 amino acid residues of any combination of F, Y, and W, such as F, FF, Y, YY, W, WW, FY, FW, YF, YW, WY, and WF. Alternatively, X1 can be a 3, 4, or 5 amino acid combination of F, Y, and W. In another preferred embodiment, the molecule comprising an aromatic ring is selected from the group of molecules comprising one or more aromatic rings which can optionally be substituted with halogen, lower alkyl, lower alkylthio, trifluoromethyl, lower acyloxy, aryl, and heteroaryl. In a most preferred embodiment, the one or more molecule comprising one or more aromatic ring comprise 9-fluorenylmethyl (Fm). Examples of such molecules include, but are not

limited to 9-fluorenylmethylcarbonyl, 9-fluorenylmethylcarbamates, 9-fluorenylmethylcarbonates, 9-fluorenylmethyl esters, 9-fluorenylmethylphosphates, and S-9-fluorenylmethyl thioethers. In embodiments wherein the molecule comprising an aromatic ring is not an amino acid, it can be attached to the polypeptide  
 5 by methods known in the art, including but not limited to, standard Fmoc protection chemistry employed in peptide synthesis.

According to other embodiments of the polypeptides of general formula I, X3 is 0, 1, 2, 3, or 4 amino acids of the sequence WLRR (SEQ ID NO:1). If X3 consists of only one amino acid of the sequence, an "R" is present, since it is the carboxy-terminal amino acid of the sequence and it would be present at the amino terminus of  
 10 the rest of the A(X4)APLP (SEQ ID NO: 2) sequence. If X3 consists of two amino acids of WLRR (SEQ ID NO:1), then the two amino acids added will be "RR". Other variations will be apparent to one of skill in the art based on the teachings herein. Similarly, variations in the residues that can make up X5 will be apparent to  
 15 one of skill in the art based on the teachings herein.

Thus, according to these various embodiments, a representative sample of polypeptides according to general formula I for use in the methods of the invention include, but are not limited to, polypeptides comprising or consisting of the following sequences: (ASAPLP)<sub>n</sub> (SEQ ID NO:3); (ATAPLP)<sub>n</sub> (SEQ ID NO:4);  
 20 (RASAPLP)<sub>n</sub> (SEQ ID NO:5); (RATAPLP)<sub>n</sub> (SEQ ID NO:6); (AYAPLP)<sub>n</sub> (SEQ ID NO:7); (RAYAPLP)<sub>n</sub> (SEQ ID NO:8); (RRASAPLP)<sub>n</sub> (SEQ ID NO:9); (LRRASAPLP)<sub>n</sub> (SEQ ID NO:10); (WLRRASAPLP)<sub>n</sub>; (SEQ ID NO:11); (RRATAPLP)<sub>n</sub> (SEQ ID NO:12); (LRRATAPLP)<sub>n</sub> (SEQ ID NO:13); (WLRRATAPLP)<sub>n</sub> (SEQ ID NO:14); (RRAYAPLP)<sub>n</sub> (SEQ ID NO:15);  
 25 (LRRAYAPLP)<sub>n</sub> (SEQ ID NO:16); (WLRRAYAPLP)<sub>n</sub> (SEQ ID NO:17); (RRASAPLPG)<sub>n</sub> (SEQ ID NO:18); (RRASAPLPD)<sub>n</sub> (SEQ ID NO:19); (RRASAPLPGL)<sub>n</sub> (SEQ ID NO:20); (RRASAPLPKG)<sub>n</sub> (SEQ ID NO:21); (RRASAPLPDL)<sub>n</sub> (SEQ ID NO:22); (RRASAPLPDK)<sub>n</sub> (SEQ ID NO:23); (RRASAPLPGLS)<sub>n</sub> (SEQ ID NO:24); (RRASAPLPGLT)<sub>n</sub> (SEQ ID NO:25);  
 30 (RRASAPLPGKS)<sub>n</sub> (SEQ ID NO:26); (RRASAPLPGKT)<sub>n</sub> (SEQ ID NO:27); (RRASAPLPDLS)<sub>n</sub> (SEQ ID NO:28); (RRASAPLPDLT)<sub>n</sub> (SEQ ID NO:29); (RRASAPLPDKS)<sub>n</sub> (SEQ ID NO:30); (RRASAPLPDKT)<sub>n</sub> (SEQ ID NO:31); (LRRASAPLPG)<sub>n</sub> (SEQ ID NO:32); (LRRASAPLPD)<sub>n</sub> (SEQ ID NO:33); (LRRASAPLPGL)<sub>n</sub> (SEQ ID NO:34); (LRRASAPLPKG)<sub>n</sub> (SEQ ID NO:35);

(LRRASAPLPDL)<sub>u</sub> (SEQ ID NO:36); (LRRASAPLPDK)<sub>u</sub> (SEQ ID NO:37);  
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(LRRASAPLPGKS)<sub>u</sub> (SEQ ID NO:40); (LRRASAPLPGKT)<sub>u</sub> (SEQ ID NO:41);  
(LRRASAPLPDLS)<sub>u</sub> (SEQ ID NO:42); (LRRASAPLPDLT)<sub>u</sub> (SEQ ID NO:43);  
5 (LRRASAPLPDKS)<sub>u</sub> (SEQ ID NO:44); (LRRASAPLPDKT)<sub>u</sub> (SEQ ID NO:45);  
(WLRRASAPLPG)<sub>u</sub> (SEQ ID NO:46); (WLRRASAPLPD)<sub>u</sub> (SEQ ID NO:47);  
(WLRRASAPLPGL)<sub>u</sub> (SEQ ID NO:48); (WLRRASAPLP GK)<sub>u</sub> (SEQ ID NO:49);  
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(LRRATAPLPDL)<sub>u</sub> (SEQ ID NO:78); (LRRATAPLPDK)<sub>u</sub> (SEQ ID NO:79);  
(LRRATAPLPGLS)<sub>u</sub> (SEQ ID NO:80); (LRRATAPLPGLT)<sub>u</sub> (SEQ ID NO:81);  
(LRRATAPLPGKS)<sub>u</sub> (SEQ ID NO:82); (LRRATAPLPGKT)<sub>u</sub> (SEQ ID NO:83);  
25 (LRRATAPLPDLS)<sub>u</sub> (SEQ ID NO:84); (LRRATAPLPDLT)<sub>u</sub> (SEQ ID NO:85);  
(LRRATAPLPDKS)<sub>u</sub> (SEQ ID NO:86); (LRRATAPLPDKT)<sub>u</sub> (SEQ ID NO:87);  
(WLRRATAPLPG)<sub>u</sub> (SEQ ID NO:88); (WLRRATAPLPD)<sub>u</sub> (SEQ ID NO:89);  
(WLRRATAPLPGL)<sub>u</sub> (SEQ ID NO:90); (WLRRATAPLP GK)<sub>u</sub> (SEQ ID NO:91);  
(WLRRATAPLPDL)<sub>u</sub> (SEQ ID NO:92); (WLRRATAPLPDK)<sub>u</sub> (SEQ ID NO:93);  
30 (WLRRATAPLPGLS)<sub>u</sub> (SEQ ID NO:94); (WLRRATAPLPGLT)<sub>u</sub> (SEQ ID  
NO:95); (WLRRATAPLPGKS)<sub>u</sub> (SEQ ID NO:96); (WLRRATAPLPGKT)<sub>u</sub> (SEQ  
ID NO:97); (WLRRATAPLPDLS)<sub>u</sub> (SEQ ID NO:98); (WLRRATAPLPDLT)<sub>u</sub>  
(SEQ ID NO:99); (WLRRATAPLPDKS)<sub>u</sub> (SEQ ID NO:100);  
(WLRRATAPLPDKT)<sub>u</sub> (SEQ ID NO:101); (RRAYAPLPG)<sub>u</sub> (SEQ ID NO:102);



(RRAYAPLPD)<sub>u</sub> (SEQ ID NO:103); (RRAYAPLPGL)<sub>u</sub> (SEQ ID NO:104);  
 (RRAYAPLP GK)<sub>u</sub> (SEQ ID NO:105); (RRAYAPLPDL)<sub>u</sub> (SEQ ID NO:106);  
 (RRAYAPLPDK)<sub>u</sub> (SEQ ID NO:107); (RRAYAPLPGLS)<sub>u</sub> (SEQ ID NO:108);  
 (RRAYAPLPGLT)<sub>u</sub> (SEQ ID NO:109); (RRAYAPLPGKS)<sub>u</sub> (SEQ ID NO:110);  
 5 (RRAYAPLPGKT)<sub>u</sub> (SEQ ID NO:111); (RRAYAPLPDLS)<sub>u</sub> (SEQ ID NO:112);  
 (RRAYAPLPDLT)<sub>u</sub> (SEQ ID NO:113); (RRAYAPLPDKS)<sub>u</sub> (SEQ ID NO:114);  
 (RRAYAPLPDKT)<sub>u</sub> (SEQ ID NO:115); (LRRAYAPLPG)<sub>u</sub> (SEQ ID NO:116);  
 (LRRAYAPLPD)<sub>u</sub> (SEQ ID NO:117); (LRRAYAPLPGL)<sub>u</sub> (SEQ ID NO:118);  
 (LRRAYAPLP GK)<sub>u</sub> (SEQ ID NO:119); (LRRAYAPLPDL)<sub>u</sub> (SEQ ID NO:120);  
 10 (LRRAYAPLPDK)<sub>u</sub> (SEQ ID NO:121); (LRRAYAPLPGLS)<sub>u</sub> (SEQ ID NO:122);  
 (LRRAYAPLPGLT)<sub>u</sub> (SEQ ID NO:123); (LRRAYAPLPGKS)<sub>u</sub> (SEQ ID NO:124);  
 (LRRAYAPLPGKT)<sub>u</sub> (SEQ ID NO:125); (LRRAYAPLPDLS)<sub>u</sub> (SEQ ID NO:126);  
 (LRRAYAPLPDLT)<sub>u</sub> (SEQ ID NO:127); (LRRAYAPLPDKS)<sub>u</sub> (SEQ ID NO:128);  
 (LRRAYAPLPDKT)<sub>u</sub> (SEQ ID NO:129); (WLRRAYAPLPG)<sub>u</sub> (SEQ ID NO:130);  
 15 (WLRRAYAPLPD)<sub>u</sub> (SEQ ID NO:131); (WLRRAYAPLPGL)<sub>u</sub> (SEQ ID NO:132);  
 (WLRRAYAPLP GK)<sub>u</sub> (SEQ ID NO:133); (WLRRAYAPLPDL)<sub>u</sub> (SEQ ID  
 NO:134); (WLRRAYAPLPDK)<sub>u</sub> (SEQ ID NO:135); (WLRRAYAPLPGLS)<sub>u</sub> (SEQ  
 ID NO:136); (WLRRAYAPLPGLT)<sub>u</sub> (SEQ ID NO:137); (WLRRAYAPLPGKS)<sub>u</sub>  
 (SEQ ID NO:138); (WLRRAYAPLPGKT)<sub>u</sub> (SEQ ID NO:139);  
 20 (WLRRAYAPLPDLS)<sub>u</sub> (SEQ ID NO:140); (WLRRAYAPLPDLT)<sub>u</sub> (SEQ ID  
 NO:141); (WLRRAYAPLPDKS)<sub>u</sub> (SEQ ID NO:142); and (WLRRAYAPLPDKT)<sub>u</sub>  
 (SEQ ID NO:143); ((F/Y/W)RRASAPLP)<sub>u</sub> (SEQ ID NO:144);  
 ((F/Y/W)LRRASAPLP)<sub>u</sub> (SEQ ID NO:145); ((F/Y/W)WLRRASAPLP)<sub>u</sub>; (SEQ ID  
 NO:146) ((F/Y/W)RRATAPLP)<sub>u</sub> (SEQ ID NO:147); ((F/Y/W)LRRATAPLP)<sub>u</sub> (SEQ  
 25 ID NO:148); ((F/Y/W)WLRRATAPLP)<sub>u</sub> (SEQ ID NO:149);  
 ((F/Y/W)RRAYAPLP)<sub>u</sub> (SEQ ID NO:150); ((F/Y/W)LRRAYAPLP)<sub>u</sub> (SEQ ID  
 NO:151); ((F/Y/W)WLRRAYAPLP)<sub>u</sub> (SEQ ID NO:152); ((F/Y/W)RRASAPLP G)<sub>u</sub>  
 (SEQ ID NO:153); ((F/Y/W)RRASAPLPD)<sub>u</sub> (SEQ ID NO:154);  
 ((F/Y/W)RRASAPLPGL)<sub>u</sub> (SEQ ID NO:155); ((F/Y/W)RRASAPLP GK)<sub>u</sub> (SEQ ID  
 30 NO:156); ((F/Y/W)RRASAPLPDL)<sub>u</sub> (SEQ ID NO:157); ((F/Y/W)RRASAPLPDK)<sub>u</sub>  
 (SEQ ID NO:158); ((F/Y/W)RRASAPLPGLS)<sub>u</sub> (SEQ ID NO:159);  
 ((F/Y/W)RRASAPLPGLT)<sub>u</sub> (SEQ ID NO:160); ((F/Y/W)RRASAPLPGKS)<sub>u</sub>; (SEQ  
 ID NO:161); ((F/Y/W)RRASAPLPGKT)<sub>u</sub> (SEQ ID NO:162);  
 ((F/Y/W)RRASAPLPDLS)<sub>u</sub> (SEQ ID NO:163); ((F/Y/W)RRASAPLPDLT)<sub>u</sub> (SEQ

**ID NO:164); ((F/Y/W)RRASAPLPDKS)<sub>u</sub> (SEQ ID NO:165);**  
**((F/Y/W)RRASAPLPDKT)<sub>u</sub> (SEQ ID NO:166); ((F/Y/W)LRRASAPLPG)<sub>u</sub> (SEQ**  
**ID NO:167); ((F/Y/W)LRRASAPLPD)<sub>u</sub> (SEQ ID NO:168);**  
**((F/Y/W)LRRASAPLPGL)<sub>u</sub> (SEQ ID NO:169); ((F/Y/W)LRRASAPLP GK)<sub>u</sub> (SEQ**  
**5 ID NO:170); ((F/Y/W)LRRASAPLPDL)<sub>u</sub> (SEQ ID NO:171);**  
**((F/Y/W)LRRASAPLPDK)<sub>u</sub> (SEQ ID NO:172); ((F/Y/W)LRRASAPLPGLS)<sub>u</sub> (SEQ**  
**ID NO:173); ((F/Y/W)LRRASAPLPGLT)<sub>u</sub> (SEQ ID NO:174);**  
**((F/Y/W)LRRASAPLPGKS)<sub>u</sub> (SEQ ID NO:175); ((F/Y/W)LRRASAPLPGKT)<sub>u</sub>**  
**(SEQ ID NO:176); ((F/Y/W)LRRASAPLPDLS)<sub>u</sub> (SEQ ID NO:177);**  
**10 ((F/Y/W)LRRASAPLPDLT)<sub>u</sub> (SEQ ID NO:178); ((F/Y/W)LRRASAPLPDKS)<sub>u</sub>**  
**(SEQ ID NO:179); ((F/Y/W)LRRASAPLPDKT)<sub>u</sub> (SEQ ID NO:180);**  
**((F/Y/W)WLRRASAPLPG)<sub>u</sub> (SEQ ID NO:181); ((F/Y/W)WLRRASAPLPD)<sub>u</sub> (SEQ**  
**ID NO:182); ((F/Y/W)WLRRASAPLPGL)<sub>u</sub> (SEQ ID NO:183);**  
**((F/Y/W)WLRRASAPLP GK)<sub>u</sub> (SEQ ID NO:184); ((F/Y/W)WLRRASAPLPDL)<sub>u</sub>**  
**15 (SEQ ID NO:185); ((F/Y/W)WLRRASAPLPDK)<sub>u</sub> (SEQ ID NO:186);**  
**((F/Y/W)WLRRASAPLPGLS)<sub>u</sub> (SEQ ID NO:187); ((F/Y/W)WLRRASAPLPGLT)<sub>u</sub>**  
**(SEQ ID NO:188); ((F/Y/W)WLRRASAPLPGKS)<sub>u</sub> (SEQ ID NO:189);**  
**((F/Y/W)WLRRASAPLPGKT)<sub>u</sub> (SEQ ID NO:190); ((F/Y/W)WLRRASAPLPDLS)<sub>u</sub>**  
**(SEQ ID NO:191); ((F/Y/W)WLRRASAPLPDLT)<sub>u</sub> (SEQ ID NO:192);**  
**20 ((F/Y/W)WLRRASAPLPDKS)<sub>u</sub> (SEQ ID NO:193); ((F/Y/W)WLRRASAPLPDKT)<sub>u</sub>**  
**(SEQ ID NO:194); ((F/Y/W)RRATAPLPG)<sub>u</sub> (SEQ ID NO:195);**  
**((F/Y/W)RRATAPLPD)<sub>u</sub> (SEQ ID NO:196); ((F/Y/W)RRATAPLPGL)<sub>u</sub> (SEQ ID**  
**NO:197); ((F/Y/W)RRATAPLP GK)<sub>u</sub> (SEQ ID NO:198); ((F/Y/W)RRATAPLPDL)<sub>u</sub>**  
**(SEQ ID NO:199); ((F/Y/W)RRATAPLPDK)<sub>u</sub> (SEQ ID NO:200);**  
**25 ((F/Y/W)RRATAPLPGLS)<sub>u</sub> (SEQ ID NO:201); ((F/Y/W)RRATAPLPGLT)<sub>u</sub> (SEQ**  
**ID NO:202); ((F/Y/W)RRATAPLPGKS)<sub>u</sub> (SEQ ID NO:203);**  
**((F/Y/W)RRATAPLPGKT)<sub>u</sub> (SEQ ID NO:204); ((F/Y/W)RRATAPLPDLS)<sub>u</sub> (SEQ**  
**ID NO:205); ((F/Y/W)RRATAPLPDLT)<sub>u</sub> (SEQ ID NO:206);**  
**((F/Y/W)RRATAPLPDKS)<sub>u</sub> (SEQ ID NO:207); ((F/Y/W)RRATAPLPDKT)<sub>u</sub> (SEQ**  
**30 ID NO:208); ((F/Y/W)LRRATAPLPG)<sub>u</sub> (SEQ ID NO:209);**  
**((F/Y/W)LRRATAPLPD)<sub>u</sub> (SEQ ID NO:210); ((F/Y/W)LRRATAPLPGL)<sub>u</sub> (SEQ**  
**ID NO:211); ((F/Y/W)LRRATAPLP GK)<sub>u</sub> (SEQ ID NO:212);**  
**((F/Y/W)LRRATAPLPDL)<sub>u</sub> (SEQ ID NO:213); ((F/Y/W)LRRATAPLPDK)<sub>u</sub> (SEQ**  
**ID NO:214); ((F/Y/W)LRRATAPLPGLS)<sub>u</sub> (SEQ ID NO:215);**

((F/Y/W)LRRATAPLPGLT)<sub>u</sub> (SEQ ID NO:216); ((F/Y/W)LRRATAPLPGKS)<sub>u</sub>  
 (SEQ ID NO:217); ((F/Y/W)LRRATAPLPGKT)<sub>u</sub> (SEQ ID NO:218);  
 ((F/Y/W)LRRATAPLPDLS)<sub>u</sub> (SEQ ID NO:219); ((F/Y/W)LRRATAPLPDLT)<sub>u</sub>  
 (SEQ ID NO:220); ((F/Y/W)LRRATAPLPDKS)<sub>u</sub> (SEQ ID NO:221);  
 5 ((F/Y/W)LRRATAPLPDKT)<sub>u</sub> (SEQ ID NO:222); ((F/Y/W)WLRRATAPLPG)<sub>u</sub>  
 (SEQ ID NO:223); ((F/Y/W)WLRRATAPLPD)<sub>u</sub> (SEQ ID NO:224);  
 ((F/Y/W)WLRRATAPLPGL)<sub>u</sub> (SEQ ID NO:225); ((F/Y/W)WLRRATAPLP GK)<sub>u</sub>  
 (SEQ ID NO:226); ((F/Y/W)WLRRATAPLPDL)<sub>u</sub> (SEQ ID NO:227);  
 ((F/Y/W)WLRRATAPLPDK)<sub>u</sub> (SEQ ID NO:228); ((F/Y/W)WLRRATAPLPGLS)<sub>u</sub>  
 10 (SEQ ID NO:229); ((F/Y/W)WLRRATAPLPGLT)<sub>u</sub> (SEQ ID NO:230);  
 ((F/Y/W)WLRRATAPLPGKS)<sub>u</sub> (SEQ ID NO:231);  
 ((F/Y/W)WLRRATAPLPGKT)<sub>u</sub> (SEQ ID NO:232); ((F/Y/W)WLRRATAPLPDLS)<sub>u</sub>  
 (SEQ ID NO:233); ((F/Y/W)WLRRATAPLPDLT)<sub>u</sub> (SEQ ID NO:234);  
 ((F/Y/W)WLRRATAPLPDKS)<sub>u</sub> (SEQ ID NO:235);  
 15 ((F/Y/W)WLRRATAPLPDKT)<sub>u</sub> (SEQ ID NO:236); ((F/Y/W)RRAYAPLPG)<sub>u</sub> (SEQ  
 ID NO:237); ((F/Y/W)RRAYAPLPD)<sub>u</sub> (SEQ ID NO:238);  
 ((F/Y/W)RRAYAPLPGL)<sub>u</sub> (SEQ ID NO:239); ((F/Y/W)RRAYAPLP GK)<sub>u</sub> (SEQ ID  
 NO:240); ((F/Y/W)RRAYAPLPDL)<sub>u</sub> (SEQ ID NO:241);  
 ((F/Y/W)RRAYAPLPDK)<sub>u</sub> (SEQ ID NO:242); ((F/Y/W)RRAYAPLPGLS)<sub>u</sub> (SEQ  
 20 ID NO:243); ((F/Y/W)RRAYAPLPGLT)<sub>u</sub> (SEQ ID NO:244);  
 ((F/Y/W)RRAYAPLPGKS)<sub>u</sub> (SEQ ID NO:245); ((F/Y/W)RRAYAPLPGKT)<sub>u</sub> (SEQ  
 ID NO:246); ((F/Y/W)RRAYAPLPDLS)<sub>u</sub> (SEQ ID NO:247);  
 ((F/Y/W)RRAYAPLPDLT)<sub>u</sub> (SEQ ID NO:248); ((F/Y/W)RRAYAPLPDKS)<sub>u</sub> (SEQ  
 ID NO:249); ((F/Y/W)RRAYAPLPDKT)<sub>u</sub> (SEQ ID NO:250);  
 25 ((F/Y/W)LRRAYAPLPG)<sub>u</sub> (SEQ ID NO:251); ((F/Y/W)LRRAYAPLPD)<sub>u</sub> (SEQ ID  
 NO:252); ((F/Y/W)LRRAYAPLPGL)<sub>u</sub> (SEQ ID NO:253);  
 ((F/Y/W)LRRAYAPLP GK)<sub>u</sub> (SEQ ID NO:254); ((F/Y/W)LRRAYAPLPDL)<sub>u</sub> (SEQ  
 ID NO:255); ((F/Y/W)LRRAYAPLPDK)<sub>u</sub> (SEQ ID NO:256);  
 ((F/Y/W)LRRAYAPLPGLS)<sub>u</sub> (SEQ ID NO:257); ((F/Y/W)LRRAYAPLPGLT)<sub>u</sub>  
 30 (SEQ ID NO:258); ((F/Y/W)LRRAYAPLPGKS)<sub>u</sub> (SEQ ID NO:259);  
 ((F/Y/W)LRRAYAPLPGKT)<sub>u</sub> (SEQ ID NO:260); ((F/Y/W)LRRAYAPLPDLS)<sub>u</sub>  
 (SEQ ID NO:261); ((F/Y/W)LRRAYAPLPDLT)<sub>u</sub> (SEQ ID NO:262);  
 ((F/Y/W)LRRAYAPLPDKS)<sub>u</sub> (SEQ ID NO:263); ((F/Y/W)LRRAYAPLPDKT)<sub>u</sub>  
 (SEQ ID NO:264); ((F/Y/W)WLRRAYAPLPG)<sub>u</sub> (SEQ ID NO:265);

((F/Y/W)WLRRAYAPLPD)<sub>u</sub> (SEQ ID NO:266); ((F/Y/W)WLRRAYAPLPGL)<sub>u</sub>  
 (SEQ ID NO:267); ((F/Y/W)WLRRAYAPLP GK)<sub>u</sub> (SEQ ID NO:268);  
 ((F/Y/W)WLRRAYAPLPDL)<sub>u</sub> (SEQ ID NO:269); ((F/Y/W)WLRRAYAPLPDK)<sub>u</sub>  
 (SEQ ID NO:270); ((F/Y/W)WLRRAYAPLPGLS)<sub>u</sub> (SEQ ID NO:271);  
 5 ((F/Y/W)WLRRAYAPLPGLT)<sub>u</sub> (SEQ ID NO:272);  
 ((F/Y/W)WLRRAYAPLPGKS)<sub>u</sub> (SEQ ID NO:273);  
 ((F/Y/W)WLRRAYAPLPGKT)<sub>u</sub> (SEQ ID NO:274);  
 ((F/Y/W)WLRRAYAPLPDLS)<sub>u</sub> (SEQ ID NO:275);  
 ((F/Y/W)WLRRAYAPLPDLT)<sub>u</sub> (SEQ ID NO:276);  
 10 ((F/Y/W)WLRRAYAPLPDKS)<sub>u</sub> (SEQ ID NO:277); and  
 ((F/Y/W)WLRRAYAPLPDKT)<sub>u</sub> (SEQ ID NO:278) wherein "u" is as defined above,  
 and (F/Y/W) means that the residue is selected from F, Y, and W. Other specific  
 polypeptides falling within the scope of general formula I will be readily apparent to  
 one of skill in the art based on the teachings herein.

15 In a further embodiment, the polypeptides according to general formula I  
 comprise a combination of different sequences from the region [X3-A (X4)APLP-X5-  
 ]<sub>u</sub>. In this embodiment, for example, the polypeptide can consist of 1 copy of SEQ ID  
 NO: 9 and 1 copy of SEQ ID NO: 143. In a different example, the polypeptide could  
 consist of 2 copies of SEQ ID NO: 200 and 3 copies of SEQ ID NO: 62. It will be  
 20 apparent to one of skill in the art that many such combinations are possible based on  
 the teachings of the present invention.

In a preferred embodiment of the polypeptides according to general formula I,  
 at least one of X2 and X6 comprises or consists of a transduction domain. As used  
 herein, the term "transduction domain" means one or more amino acid sequences that  
 25 can carry the active domain across cell membranes. These domains can be linked to  
 other polypeptides to direct movement of the linked polypeptide across cell  
 membranes. In some cases the transducing molecules do not need to be covalently  
 linked to the active polypeptide (for example, see sequence ID 291). In a preferred  
 embodiment, the transduction domain is linked to the rest of the polypeptide via  
 30 peptide bonding. (See, for example, (9, 8, 6, 16, 19, 10) ). In this embodiment, any of  
 the polypeptides as described above would include at least one transduction domain.  
 In a further embodiment, both X2 and X6 comprise transduction domains. In a  
 further preferred embodiment, the transduction domain(s) is/are selected from the  
 group consisting of (R)<sub>4-9</sub> (SEQ ID NO:279); GRKKRRQRRRPPQ (SEQ ID

NO:280); YARAAARQARA (SEQ ID NO:281);  
 DAATATRGRSAASRPTERPRAPARSASRPRRPVE (SEQ ID NO:282);  
 GWTLNSAGYLLGLINKALAALAKKIL (SEQ ID NO:283); PLSSIFSRIGDP  
 (SEQ ID NO:284); AAVALLPAVLLALLAP (SEQ ID NO:285);  
 5 AAVLLPVLLAAP (SEQ ID NO:286); VTVLALGALAGVGVG (SEQ ID  
 NO:287); GALFLGWLGAAGSTMGAWSQP (SEQ ID NO:288);  
 GWTLNSAGYLLGLINKALAALAKKIL (SEQ ID NO:289);  
 KLALKLALKALKAALKLA (SEQ ID NO:290);  
 KETWWETWWTEWSQPKKKRKV (SEQ ID NO:291); KAFAKLAARLYRKAGC  
 10 (SEQ ID NO:292); KAFAKLAARLYRAAGC (SEQ ID NO:293);  
 AAFAKLAARLYRKAGC (SEQ ID NO:294); KAFAALAARLYRKAGC (SEQ ID  
 NO:295); KAFAKLAAQLYRKAGC (SEQ ID NO:296), and  
 GGGGYGRKKRRQRRR (SEQ ID NO:297).

The polypeptides of the invention according to general formula II recite that J4  
 15 is S, T, Y, D E, a phosphoserine mimic, or a phosphotyrosine mimic. It is preferred  
 that J4 is S, T, or Y; more preferred that J4 is S or T, and most preferred that J4 is S.  
 In these embodiments where J4 is S, T, or Y, it is most preferred that J4 is  
 phosphorylated. When J4 is D or E, these residues have a negative charge that  
 mimics the phosphorylated state. The polypeptides according to general formula II  
 20 are optimally effective in the methods of the invention when J4 is phosphorylated, is a  
 phosphoserine or phosphotyrosine mimic, or is another mimic of a phosphorylated  
 amino acid residue, such as a D or E residue. Examples of phosphoserine mimics  
 include, but are not limited to, sulfo-serine, amino acid mimics containing a methylene  
 substitution for the phosphate oxygen, 4-phosphono(difluoromethyl)phenylalanine,  
 25 and L-2-amino-4-(phosphono)-4,4-difluorobutanoic acid. Other phosphoserine  
 mimics can be made by those of skill in the art; for example, see (15). Examples of  
 phosphotyrosine mimics include, but are not limited to,  
 phosphonomethylphenylalanine, difluorophosphonomethylphenylalanine, fluoro-O-  
 malonyltyrosine and O-malonyltyrosine. (See, for example, (1)).

30 In a further preferred embodiment of the polypeptides according to general  
 formula II, at least one of J2 and J6 comprises or consists of a cell transduction  
 domain. In a further preferred embodiment, the carboxy-terminal end of the  
 polypeptides according to general formula II are unblocked. In a further preferred

embodiment, the amino terminal end of the polypeptides according to general formula II are unblocked.

The HSP20 polypeptide sequence is as follows (SEQ ID NO: 298):

Met Glu Ile Pro Val Pro Val Gln Pro Ser Trp Leu Arg Arg Ala Ser Ala Pro Leu Pro  
 5 Gly Leu Ser Ala Pro Gly Arg Leu Phe Asp Gln Arg Phe Gly Glu Gly Leu Leu Glu  
 Ala Glu Leu Ala Ala Leu Cys Pro Thr Thr Leu Ala Pro Tyr Tyr Leu Arg Ala Pro Ser  
 Val Ala Leu Pro Val Ala Gln Val Pro Thr Asp Pro Gly His Phe Ser Val Leu Leu Asp  
 Val Lys His Phe Ser Pro Glu Glu Ile Ala Val Lys Val Val Gly Glu His Val Glu Val  
 His Ala Arg His Glu Glu Arg Pro Asp Glu His Gly Phe Val Ala Arg Glu Phe His Arg  
 10 Arg Tyr Arg Leu Pro Pro Gly Val Asp Pro Ala Ala Val Thr Ser Ala Leu Ser Pro Glu  
 Gly Val Leu Ser Ile Gln Ala Ala Pro Ala Ser Ala Gln Ala Pro Pro Pro Ala Ala Ala  
 Lys.

The polypeptides may be subjected to conventional pharmaceutical operations  
 such as sterilization and/or may contain conventional adjuvants, such as preservatives,  
 15 stabilizers, wetting agents, emulsifiers, buffers etc.

For administration, the polypeptides are ordinarily combined with one or more  
 adjuvants appropriate for the indicated route of administration. The compounds may  
 be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids,  
 stearic acid, talc, magnesium stearate, magnesium oxide, sodium and calcium salts of  
 20 phosphoric and sulphuric acids, acacia, gelatin, sodium alginate, polyvinylpyrrolidone,  
 dextran sulfate, heparin-containing gels, and/or polyvinyl alcohol, and tableted or  
 encapsulated for conventional administration. Alternatively, the compounds of this  
 invention may be dissolved in saline, water, polyethylene glycol, propylene glycol,  
 carboxymethyl cellulose colloidal solutions, ethanol, corn oil, peanut oil, cottonseed  
 25 oil, sesame oil, tragacanth gum, and/or various buffers. Other adjuvants and modes of  
 administration are well known in the pharmaceutical art. The carrier or diluent may  
 include time delay material, such as glyceryl monostearate or glyceryl distearate alone  
 or with a wax, or other materials well known in the art.

The polypeptides or pharmaceutical compositions thereof may be administered  
 30 by any suitable route, including orally, parentally, by inhalation spray, rectally, or  
 topically in dosage unit formulations containing conventional pharmaceutically  
 acceptable carriers, adjuvants, and vehicles. The term parenteral as used herein

includes, subcutaneous, intravenous, intra-arterial, intramuscular, intrasternal, intratendinous, intraspinal, intracranial, intrathoracic, infusion techniques or intraperitoneally. Preferred embodiments for administration vary with respect to the condition being treated, and are described in detail below.

5           The polypeptides may be made up in a solid form (including granules, powders or suppositories) or in a liquid form (*e.g.*, solutions, suspensions, or emulsions). The polypeptides of the invention may be applied in a variety of solutions. Suitable solutions for use in accordance with the invention are sterile, dissolve sufficient amounts of the polypeptides, and are not harmful for the proposed  
10       application.

          In Experiments described herein it is demonstrated that treatment of neonatal ventricular tissue with sodium nitroprusside leads to increases in the rate of contraction and increased phosphorylation of HSP20. The addition of phosphopeptide analogues of HSP20 into transiently permeabilized cardiac myocytes led to increases  
15       in the rate of contraction of the myocytes. These results are consistent with previously reported findings demonstrating that the NO-cGMP pathway increases beat rate by stimulating the hyperpolarization-activated pacemaker current *I<sub>f</sub>* (14). While not being bound by any specific mechanism of action, the present results suggest that the mechanism of NO stimulation of heart rate via *I<sub>f</sub>* involves phosphorylation of HSP20  
20       and that phosphorylated HSP20 may have a direct effect on *I<sub>f</sub>* channels. The increased rate of contraction was also related to increases in the rate of relaxation of the myocytes. Consistent with this increase, is an increase in the rate of decline of the  $\text{Ca}^{2+}$  transient. While not being bound by any specific mechanism of action, these data suggest that phosphorylated HSP20 facilitates increased beat rate by stimulating  
25       a more rapid uptake of  $\text{Ca}^{2+}$  by the SR, and further suggest that HSP20 may have a direct role in modulating the lusitropic actions of nitric oxide and nitric oxide donors.

          HSP20 is biochemically associated with  $\alpha$ B-crystallin and co-localizes with  $\alpha$ B-crystallin and sarcomeric actin at the I-band. The association of HSP20 and  $\alpha$ B-crystallin with the I-band suggests that these two small heat shock proteins may be  
30       involved in modulating cytoskeletal and/or contractile dynamics of cardiac myocytes.

## Examples

### Example 1

*Materials:* Sodium dodecylsulfate (SDS); glycine; and tris-(hydroxymethyl) aminomethane (Tris); dithiothreitol (DTT); were from Research Organics (Cleveland, OR). Coomassie brilliant blue was from ICN Biomedicals Inc (Aurora, OR). Recombinant HSP27 was from StressGen (Victoria, BC Canada). Recombinant HSP20 was produced as previously described<sup>14</sup>. Piperazine diacrylamide and other electrophoresis/ reagents were from Biorad (Hercules, CA). 3-((3-cholamidopropyl dimethyl ammonio)-1-propanesulfonate (CHAPS); ethylene glycol bis (B-aminoethyl ether) - N, N, N' - tetra acetic acid (EGTA); ethylene diaminetetraacetic acid (EDTA); polyoxyethylene-sorbitan monolaurate (Tween-20); purified bovine  $\alpha$ B-crystallin; sodium nitroprusside and all other reagent grade chemicals were from Sigma (St. Louis, MO). Molecular weight standards were from Pharmacia (Upsalla, Sweden). Immobilon was from Millipore (Bedford Ma). Antibodies against sarcomeric actin were from Sigma (St. Louis, Mo), HSP20 and  $\alpha$ B-crystallin from Dr. Kanefusa Kato (Aichi, Japan) (12), HSP25 from Dr Michael Welsh (University of Michigan, Ann Arbor Michigan) (20) Accurate (Westbury, NY.), Stressgen (Victoria, BC) and myotonic dystrophy kinase binding protein from Dr. Atshushi Suzuki (Yokohama, Japan) (18). Goat anti-mouse and anti-rabbit secondary antibodies were from Jackson Immunochemical (West Grove, PA). Protein concentrations were determined using the Coomassie Plus Protein Assay Reagent (Pierce Rockford IL).

*Isolation of rat heart tissue:* Adult rats (2-3 months of age) were sacrificed with CO<sub>2</sub> inhalation and the hearts were dissected free from the thoracic cavity and placed in phosphate buffered saline (PBS, 10 mM phosphate, pH 7.5, 0.15 M NaCl, 4°C). The atria were dissected free and the ventricle was, cut into small strips, and homogenized for biochemical analyses. For immunohistochemical analyses, the thoracic aorta was cannulated and perfused with PBS followed by 4% formalin in PBS at 100 mmHg. Ventricular myocytes were isolated from the hearts of 2 day old Sprague- Dawley rats by gentle trypsinization and placed in culture as previously described (11). Animal use was approved by the Institutional Animal Care and Use Committee.

*Immunoblotting:* Tissues were homogenized in 10 mM EGTA, 2 mM EDTA, 10 mM  $\beta$ -mercaptoethanol, 1 % Glycerol, and 4% SDS in 60 mM Tris, pH 7.0 followed



by centrifugation (10 000 x g) to remove insoluble material. Proteins were separated on 15% SDS-PAGE gels and transferred to Immobilon for 210volt hours. The blots were air dried and subsequently blocked with tris buffered saline (TBS: 10 mM Tris, 150 mM NaCl pH 7.4)/ 5% milk for 1 hour. The blots were then incubated with anti-  
5 HSP20 (1-/1000), anti- $\alpha$ B-crystallin (1/1000), anti-HSP25 (1/1000) or anti-MKBP (1/1000) antibodies in TBS/milk for one hour at room temperature. The blots were washed 3 times (5 minutes each) in TBS/Tween-20 (0. 5%). The blots were then placed in goat anti-rabbit secondary antibody diluted in TBS/milk (1/2000) for one hour at room temperature. The blots were then washed 6 times (5 minutes each) in  
10 TBS/Tween-20. Immunoreactive protein was determined using enhanced chemiluminescence (DuPont NEN, Boston, MA) exposed on X-ray film.

*Subcellular fractionation:* Tissues were homogenized in homogenization buffer ("HEPES buffer" 25 mM HEPES, 150 mM NaCl, 10 mM EDTA, 1 mM DTT, 2 mM benzamidine, pH 7.4 (0. 5 gm tissue/1 ml buffer)) in a polytron homogenizer at 4°C.  
15 The homogenate was centrifuged 3000 x g to remove debris and the nuclear pellet. The supernatants were diluted to 5  $\mu$ g of protein/ $\mu$ l and 250  $\mu$ l of supernatant was centrifuged 10,000 x g for 10 minutes. The pellet (P 1) was resuspended in 125  $\mu$ l of homogenization buffer and 125  $\mu$ l of 2X sample buffer (6.25 mM Tris pH 6.8, 2% SDS, 5% 2- $\beta$ -mercaptoethanol, 10% glycerol, 0.025% bromophenol blue). To 125  $\mu$ l  
20 of the 10,000 x g supernatant (S1), 125  $\mu$ l of 2X sample buffer was added. The remaining 125  $\mu$ l of 10,000 x g supernatant was centrifuged 100,000 x g. The 100,000 x g pellet (P2) was resuspended in 125  $\mu$ l of homogenization buffer and 125  $\mu$ l of 2X sample buffer. 125  $\mu$ l of 2X sample buffer was added to the 100,000 x g supernatant (S2). The samples were boiled for 8 minutes after the addition of sample buffer,  
25 separated on 15% SDS-PAGE gels, transferred to Immobilon membranes and probed with anti-actin antibodies (1/2000 dilution), anti-HSP20 antibodies (1/2000 dilution), anti- $\alpha$ B-crystallin antibodies (1/2000 dilution) and anti-MKBP antibodies (1/2000 dilution).

*Gel Filtration:* Gel filtration was performed as previously described (3). In  
30 brief, the tissues were homogenized in HEPES buffer (0. 5 gm tissue/1 ml buffer) at 4°C using a polytron homogenizer (Brinkman Instruments, Westbury, NY). The homogenate was centrifuged 100,000 X g for 30 minutes at 4°C. 200  $\mu$ l of

supernatant (containing 200 µg total protein) was applied to a Superose- HR 10/30 fast protein liquid chromatography column (Pharmacia, Upsalla Sweden), eluted with column buffer and 0.5 ml fractions collected. For calibration, 10 µl of catalase (232 kDa, 5 mg/ml) and bovine serum albumin (67 kDa, 8 mg/ml) were applied to the column.

*Dot blotting:* 100 µl of each fraction from the column was dot blotted onto nitrocellulose. The blots were fixed with 20% methanol, dried, blocked with TBS, 5% milk, for 1 hour, washed 3 times with TBS, and then probed with anti-HSP20, anti-MKBP, and anti- αB-crystallin antibodies (1/2000 dilution in TBS, 5% milk) for 1 hour. Goat anti-rabbit secondary antibodies (1/2000 dilution) were added to the blots for one hour. The blots were then washed 6 times with TBS/0.5% Tween-20. Immunoreactive proteins were visualized as described above with enhanced chemiluminescence and densitometric analysis was performed using UN-SCAN-IT automated digitizing software (Silk Scientific Corporation, Orem, UT).

*Immunohistochemistry:* Perfusion fixed ventricular tissue was embedded in paraffin. Five micron cross-sections were mounted on polylysine slides. The slides were de-paraffinized with xylene and graded dilutions of ethanol. The sections were rinsed in PBS and blocked with donkey serum (Jackson ImmunoResearch, West Grove, PA.) for 30 minutes. The slides were then incubated with anti-HSP20 (1/100), anti-αB-crystallin (1/100), anti-sarcomeric actin (1/100), or anti-MKBP (1/100) overnight at 4°C. The slides were then washed with PBS, 4 times (15 minutes each), at room temperature. Anti-mouse and anti-goat Cy3 secondary antibodies (1/100) were used to detect immunoreactive protein. The sections were imaged on a Zeiss Axiophot microscope interfaced with a SPOT camera (Diagnostic Instruments, Sterling Heights, Michigan) and a Gateway computer (N. Sioux City, SD).

*Two-dimensional gels:* Tissues were snap frozen in liquid nitrogen and ground to a fine powder using mortar and pestle. The proteins were solubilized in 100 mM DTT, 6 M Urea, 2% CHAPS overnight. 30 µg of protein was loaded onto 12 x 15 cm slab isofocusing gels consisting of 4% acrylamide, 0.1% piperazine diacrylamide, 9 M urea, 5 % ampholines (5 parts 6-8, 3 parts 5-7, and 2 parts 3-10), 2% CHAPS. The cathode buffer consisted of 20 mM sodium hydroxide and the anode buffer 10 mM

phosphoric acid. The proteins were focused for 10,000 volt hours. The gels were fixed in 10% trichloroacetic acid and stained overnight with NeuHoff's Coomassie stain. The lanes of stained proteins were cut from the isofocusing slab gels and equilibrated in 10 mM Tris (pH 6.8), 3% SDS, 19 % ethanol, 4%  $\beta$ -mercaptoethanol, and 0.004% bromophenol blue, for 10 minutes. The proteins were then separated on 12% acrylamide SDS gels and transferred to Immobilon 100 mÅmp for 12 hours. The blots were probed for HSP20 as described above. The isoelectric focusing gradient was determined with BioRad IEF standards.

*Peptide sequencing:* The peptides, HSP20 phospho serine analogue N-WLRRASphosAPLPGLK (HSP20-PS) and a scrambled phosphorylated peptide N-PRKSphosLWALGRPLA (HSP20-SC) were synthesized on a Procise (Applied Biosystems, Model 492) instrument using standard protocols. The peptides were purified using high pressure liquid chromatography and purity was assured with mass spectrometry as previously described.

*Permeabilization of Cardiac Myocyte:* Permeabilization of cardiac myocytes was performed as described (11). Briefly, cells were slowly cooled by sequential two minute incubations with room temperature PBS then with 40°C PBS in an ice bath for two minutes. The PBS was discarded, and the cells were incubated with ATP (30  $\mu$ l of 200mmol/L ATP, pH 7.4) followed immediately by permeabilization buffer (20 mmol/L HEPES, pH 7.4, 10 mmol/L EGTA, 140 mmol/L KCl, 50g/mL saponin, 5mmol/L oxalic acid dipotassium salt) containing the peptides (10 $\mu$ M) for 10 minutes in an ice bath. The cells were then washed four times on ice with chilled PBS. The cells were then returned to 37°C by incubations with room temperature PBS and 37°C PBS. The original cell media was then added at 37 °C.

*Measurement of Cardiac Myocyte Contraction Rate/Relaxation Rate:* The culture dishes containing the myocytes were placed on a Harvard Apparatus temperature regulation device positioned on the stage of an inverted microscope (Carl Zeiss Inc., Munchen- Hallbergmoos, Germany) and maintained at 37°C with a jacketed water bath. The microscope was outfitted with a digital camera and Video Savant software. To determine the effects of HSP20 peptide analogues on contractile rate, individual cells were monitored before and after permeabilization. Contractile rates were

determined every 2 minutes (for a 15 second period) for a total of 10 minutes. Images of individual cells were captured at 30 frames/second.

*Calcium Transients:*  $\text{Ca}^{2+}$  transients were measured as previously described in detail elsewhere with only minor modifications (4). For these experiments myocytes were  
5 cultured on 25 mm glass coverslips. Following permeabilization (as described above), each coverslip was mounted in a leak-proof circular holding chamber (Medical Systems Inc., Cambridge MA) and gently washed several times with a Ringer solution containing: 142. mM NaCl, 4.0 mM KCl, 1.8 mM  $\text{MgCl}_2$ , 1.8 mM  $\text{CaCl}_2$ , 5.0 mM N-2-hydroxyethylpiperazine-N-2-ethanesulfonic acid (HEPES, pH 7. 0), and 5.0 mM  
10 glucose. After washing, the myocytes were incubated in 1 ml Ringer solution with 1  $\mu\text{M}$  fura-2 AM for 10 minutes at 37°C in a rotating water bath. The myocytes were subsequently washed several times with dye-free Ringer solution and allowed to stand covered at room temperature for 30 minutes to facilitate de-esterification.

Fluorescence measurements in individual rhythmically beating myocytes were  
15 carried out at 37°C using a DeltaScan microspectrofluorometer (Photon Technology International, NJ) coupled to an Olympus IX70 microscope equipped with an Olympus UApo/340 40X oil immersion objective with a numerical aperture of 1.35. The fura-2 transients reported are the ratio of  $\text{Ca}^{2+}$  fluorescence transients measured at excitation wavelengths 340 and 380 nm. The myocytes were only illuminated at short  
20 intervals, and each sample preparation was used for less than 1 hr to reduce the possibility of photobleaching or fura-2 leakage.

*Statistical Analysis:* Values are reported as mean +/- SEM, and "n" refers to the number animals examined. The statistical differences between two groups was determined with student's t test and between multiple groups with one way repeated  
25 measures analysis of variance (ANOVA) using Sigma Stat software (Jandel Scientific, San Rafael, CA). A p-value less than 0.05 was considered significant.

## Example 2

This example illustrates the specificity of small HSP antibodies. The small heat shock proteins are highly homologous. Thus, to determine the specificity of the  
30 antibodies, immunoblots of recombinant HSP20, recombinant HSP25, bovine lens  $\alpha\text{B}$ -crystallin, and homogenized rat heart were probed. Rat heart tissue homogenates (100  $\mu\text{g}$ ), bovine  $\alpha\text{B}$ -crystallin (1  $\mu\text{g}$ ), recombinant HSP25 (1  $\mu\text{g}$ ), and recombinant

HSP20 (1  $\mu$ g) were separated by SDS-PAGE and transferred to Immobilon as described in the materials and methods. The blots were then probed with anti-HSP20 antibodies (1: 1000 dilution), anti- $\alpha$ B-crystallin antibodies (1: 1000 dilution) or anti-MKBP antibodies (1: 1000 dilution).

5           The HSP20,  $\alpha$ B-crystallin, and MKBP antibodies recognized only the corresponding purified or recombinant protein. The anti-HSP20 antibodies recognized a major band at 20 kDa with a smaller band at a slightly lower relative mobility in heart homogenate proteins. This additional lower band may represent cross-reactivity with other proteins or may represent HSP20 that has been post translationally  
10   modified (eg. phosphorylated and nonphosphorylated HSP20). The anti- $\alpha$ B-crystallin antibodies recognized a single band with a relative mobility of 20 kDa in heart homogenates. The anti-MKBP antibodies recognized a band with a relative mobility of 20 kDa and another band with a higher relative mobility (approximately 35 kDa) in heart homogenates. The additional band may represent cross-reactivity with other  
15   proteins. There were very low levels of immunoreactive HSP25 in adult rat heart using an affinity purified mouse monoclonal antibody (20) or commercially available antibodies. These commercially available antibodies all recognized recombinant HSP25. Thus, only the associations between HSP20,  $\alpha$ B-crystallin, and MKBP were examined in subsequent studies.

### 20   **Example 3**

          This example illustrates the subcellular localization and macromolecular associations of the small HSPs. To determine the intracellular distribution of the small heat shock proteins in cardiac myocytes, subcellular fractionation was performed as described in the materials and methods. Rat heart tissues were homogenized as  
25   described in the materials and methods. Blots were prepared with lanes containing proteins from the 10,000 x g supernatant, 10,000 x g pellet, 100,000 x g supernatant, and 100,000 x g pellet. The blots were probed with anti-HSP20 antibodies (1:1000 dilution), anti- $\alpha$ B-crystallin antibodies (1:1000 dilution), or anti- MKBP antibodies (1:1000 dilution).

30           The data from these experiments showed that HSP20 and MKBP were in the cytosolic fraction in rat heart homogenates.  $\alpha$ B-crystallin was predominantly in the

cytosolic fraction but there was also a minor component of immunoreactive  $\alpha$ B-crystallin in the particulate fraction.

Since the small HSPs were predominantly cytosolic proteins, gel filtration was performed on the cytosolic fractions of rat heart muscle homogenates using a molecular sieving column (Superose 6). Fractions from the column were dot blotted with antibodies against HSP20,  $\alpha$ B-crystallin, and MKBP. HSP20 and  $\alpha$ B-crystallin were found in similar fractions that eluted from the column after the catalase standard (MW 232 kDa). MKBP eluted from the column in the same fraction as the bovine serum albumin standard (MW 67 kDa).

These data demonstrate that HSP20 and  $\beta$ -crystallin are associated in macromolecular aggregates in cardiac myocytes.

#### Example 4

This example illustrates the cellular localization of the small HSP's using immunofluorescence microscopy. Rat hearts were perfusion fixed and sections were stained with anti-sarcomeric actin antibodies (1:100 dilution), anti  $\alpha$ B-crystallin antibodies (1:100 dilution), anti-HSP20 antibodies (1:100 dilution), or anti-MKBP antibodies (1:100 dilution). Cy3 conjugated secondary antibodies were used and the slides were imaged with a fluorescence microscope (magnification, 63X).

Immunoreactive sarcomeric actin was present in distinct transverse bands. Immunoreactive  $\alpha$ B-crystallin was also present in transverse bands but the staining was more punctate. Immunoreactive HSP20 was present in transverse bands and there was also staining of the cell membranes. Immunoreactive MKBP staining was less distinct, but there appeared to be longitudinal band-like staining with a distinct lack of immunoreactive staining for MKBP at the intercalated discs. Immunoreactive HSP25 was not detected using any of the 4 HSP25 antibodies tested. There was no specific pattern of immunoreactivity using pre-immune serum or no primary antibody.

These data demonstrate that crystalline and HSP20 have a staining pattern of distinct transverse bands similar to the pattern observed after staining for sarcomeric actin. This suggests that HSP20 is localized to the actin sarcomere.

#### Example 5

This example illustrates that activation of cyclic nucleotide signaling pathways leads to increases in the phosphorylation of HSP20 in cardiac myocytes. To determine

if activation of cyclic nucleotide signaling pathways led to increases in the phosphorylation of HSP20, two-dimensional immunoblotting was performed. Increases in the phosphorylation of HSP20 in vascular smooth muscle led to a shift of HSP20 from a basic to more acidic isoforms (2).

5 Rat cardiac myocytes were equilibrated in bicarbonate buffer for one hour. The myocytes were then treated with buffer alone or with the NO donor, sodium nitroprusside (10  $\mu$ M, 10 minutes). The cells were then homogenized, solubilized then separated by 2-dimensional electrophoresis. The proteins were then transferred to Immobilon then probed with anti-HSP20 antibodies (1:1000 dilution).

10 Blots from cells treated with buffer alone demonstrated a single point of immunoreactive protein with a relative mobility of 20 kDa and an isoelectric focusing point of 6.5. Blots from strips treated with sodium nitroprusside demonstrated a single point of immunoreactive protein with a relative mobility of 20 kDa and an isoelectric focusing point of 5.6. These isoelectric values are consistent with non-phosphorylated and phosphorylated HSP20 respectively.

#### Example 6

This example illustrates that phosphorylated peptide analogues of HSP20 led to increase in the contractile rate of cardiac myocytes. To determine if HSP20 has a direct role in myocyte function, a model of transient permeabilization of cultured myocytes was used (11). The basal contractile rate of cardiac myocytes was determined using computer-assisted digital microscopy imaging techniques. The cells were then transiently permeabilized and incubated with N-PRKSphosLWALGRPLA (SEQ ID NO:299) (SC, a scrambled phosphorylated peptide) or with N-WLRRASphosAPLPGLK (PS, the phosphoHSP20 peptide analogue) (SEQ ID NO:300). Following permeabilization, the cells were placed back on the microscope stage and the contractile rate was again determined. The data represent the % increase in contraction rate over basal rate (%increase in rate, n=25 cells per group from 5 different experiments, \* = P<0.05). Using a digital camera and Video Savant software, images of individual cells were captured at 30 frames/second before and after permeabilization and introduction of the PS peptide analogue.

30 Introduction of the phosphorylated peptide analogue of HSP20 (SEQ ID NO:300) resulted in a significant increase in the rate of cardiac myocyte contraction (37.6% +/- 2.4%). Similar increases in the rate of contraction occurred after treatment

with sodium nitroprusside (10  $\mu$ M, 33. 5% +/- 5.3%). In experiments where the myocytes were permeabilized in the absence of peptides (1. % +/- 0.5% increase) or scrambled phosphorylated peptides (5.9% +/- 1.9% increase) (SEQ ID NO:299), there was no significant change in the contractile rate.

- 5 Since phosphorylated HSP20 is associated with relaxation of vascular smooth muscle, we hypothesized that phosphopeptide analogues of HSP20 (SEQ ID NO:300) increased cardiac myocyte contractile rate by increasing their relaxation rate. To determine the rate of relaxation of the cardiac myocytes, contractile properties were analyzed using a digital camera and Video Savant software. The times for contraction
- 10 and relaxation were measured before and after transient permeabilization in the presence of peptide analogues. There was a 50% increase in the time of relaxation in the cells exposed to the phosphopeptide analogue of HSP20 (SEQ ID NO:300). The relaxation time went from 0.06 seconds to 0.03 seconds. There were no significant changes in the relaxation rate in myocytes permeabilized in the absence of peptide, (0.
- 15 058 +/- 0.005 s) or incubated in the presence of the scrambled phosphorylated peptide (0.055 +/- 0.006s).

#### Example 7

- We next examined  $\text{Ca}^{2+}$  fluxes in transiently permeabilized myocytes using the  $\text{Ca}^{2+}$  fluoroprobe, fura-2. Myocytes cultured on glass coverslips were
- 20 permeabilized in the presence of a phosphopeptide analogue of HSP20 (WLRRASAPLPGLK with a phosphoserine, SEQ ID NO:300) or scrambled phosphopeptides (PRKSLWALGRPLA with a phosphoserine SEQ ID NO:299) or permeabilized in the absence of peptides just prior to loading with fura-2 AM. Data were collected from individual rhythmically beating myocytes (ratio of light emitted
- 25 at 510 nm when alternately excited at 340 and 380 nm). For each myocyte, data were collected for 20 - 25 seconds and used only if the basal level and the peak magnitudes of the  $\text{Ca}^{2+}$  transients remained stable over this period. For each data set, the time constants for the decay ( $\tau$ ) were determined for 5 consecutive  $\text{Ca}^{2+}$  transients and averaged. The data were collected from 16 - 23 myocytes per group in 3 separate
- 30 experiments (see text; \* =P < 0. 05).

The results demonstrated a significant decrease in the time constant for exponential ( $\tau$ ) decay of the  $\text{Ca}^{2+}$  transients in the phosphoserine group that was permeabilized with the phosphopeptide analogue of HSP20 (0.104 +/- 0.005 sec., n =



16) compared to the group treated with the scrambled phosphopeptide (0.236 +/- 0.011 sec., n = 18) or the myocytes permeabilized in the absence of any phosphopeptide (0.242 +/- 0.021 sec., n = 23), when determined by fitting the declining phase of the transient by a first order exponential. There was not a significant difference when comparing the  $\tau$  decay in myocytes treated with scrambled phosphopeptide to the myocytes permeabilized in the absence of peptide. The decreased  $\tau$  decay of the  $\text{Ca}^{2+}$  transient in the presence of phosphopeptide HSP20 analogue was consistent with the observation described above that demonstrated an increased rate of contractile relaxation when measured with digital photography. Moreover, the more rapid decline of the  $\text{Ca}^{2+}$  transient suggests that the increased relaxation rate is due to more rapid uptake of  $\text{Ca}^{2+}$  by the sarcoplasmic reticulum (SR).

There were no differences in the peak systolic  $\text{Ca}^{2+}$  transients when myocytes that contained the HSP20 phosphopeptide analogue were compared to the scrambled phosphopeptide ( $P > 0.05$ ). However, the permeabilization with either of the phosphopeptides resulted in a decrease in the peak magnitude of the  $\text{Ca}^{2+}$  transient that was evident when comparing myocytes permeabilized with scrambled phosphopeptide (1.05 +/- 0.02 340/380 ratio units) or phosphopeptide HSP20 analogue (1.01 +/- 0.02) to permeabilized myocytes in the absence of peptide (1.16 +/- 0.02;  $P < 0.05$ ). These data indicated that permeabilization with phosphopeptides resulted in a non-specific decrease in the magnitude of the transients. The diastolic  $\text{Ca}^{2+}$  level was not significantly different in any of the three groups. From these data it can be concluded that phosphorylation of HSP20 does not specifically affect the magnitude of the  $\text{Ca}^{2+}$  transient.

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**We claim:**

1 1. A method for increasing the contractile rate in heart muscle comprising  
2 administering to an individual in need thereof an amount effective to increase the  
3 contractile rate in heart muscle of one or more polypeptides comprising a sequence  
4 according one or more of:

5 (a) general formula I:

6  $X1-X2-[X3-A(X4)APLP-X5]_u-X6$

7 wherein X1 is absent or is one or more molecules comprising one or more  
8 aromatic ring;

9 X2 is absent or comprises a transduction domain;

10 X3 is 0, 1, 2, 3, or 4 amino acids of the sequence WLRR (SEQ ID NO:1);

11 X4 is selected from the group consisting of S, T, Y, D, E, hydroxylysine,  
12 hydroxyproline, phosphoserine analogs and phosphotyrosine analogs;

13 X5 is 0, 1, 2, or 3 amino acids of a sequence of genus Z1-Z2-Z3,

14 wherein Z1 is selected from the group consisting of G and D;

15 Z2 is selected from the group consisting of L and K; and

16 Z3 is selected from the group consisting of S, T, and K;

17 X6 is absent or comprises a transduction domain; and

18 wherein u is 1-5; and

19 (b) general formula II:

20  $J1-J2-[J3-A(J4)APLP-J5]_u-J6$

21 wherein J1 is absent or is one or more molecules comprising one or more  
22 aromatic ring;

23 J2 is absent or comprises a cell transduction domain;

24 J3 is 0-14 amino acids of the sequence of heat shock protein 20 between  
25 residues 1 and 14 of SEQ ID NO:298;

26 J4 is selected from the group consisting of S, T, Y, D, E, hydroxylysine,  
27 hydroxyproline, phosphoserine analogs and phosphotyrosine analogs;

28 J5 is 0-140 amino acids of heat shock protein 20 between residues 21 and 160  
29 of SEQ ID NO:298; and

30 J6 is absent or comprises a cell transduction domain.

- 1 2. The method of claim 1 wherein increasing the contractile rate in heart muscle  
2 comprises decreasing the heart muscle relaxation rate.
- 1 3. The method of claim 1 wherein the individual suffers from one or more of  
2 bradyarrhythmia, bradycardia, congestive heart failure, stunned myocardium,  
3 pulmonary hypertension, and diastolic dysfunction.
- 1 4. The method of claim 1 wherein the one or more polypeptides comprise a  
2 sequence according to general formula I.
- 1 5. The method of claim 1 wherein the one or more polypeptides comprise a  
2 sequence according to general formula II.
- 1 6. The method of claim 1 wherein the one or more polypeptides consists of a  
2 sequence according to general formula I.
- 1 7. The method of claim 1 wherein the one or more polypeptides consists of a  
2 sequence according to general formula II.
- 1 8. The method of claim 4 wherein at least one of X2 and X6 comprises a  
2 transduction domain.
- 1 9. The method of claim 5 wherein at least one of J2 and J6 comprises a  
2 transduction domain.
- 1 10. A method for treating a heart muscle disorder comprising administering to an  
2 individual suffering from one or more of bradyarrhythmia, bradycardia, congestive  
3 heart failure, stunned myocardium, pulmonary hypertension, and diastolic dysfunction  
4 an amount effective to increase heart muscle contractile rate of one or more  
5 polypeptides comprising a sequence according one or more of:
- 6 (a) general formula I:  
7  $X1-X2-[X3-A(X4)APLP-X5]_n-X6$   
8 wherein X1 is absent or is one or more molecules comprising one or more  
9 aromatic ring;  
10 X2 is absent or comprises a transduction domain;  
11 X3 is 0, 1, 2, 3, or 4 amino acids of the sequence WLRR (SEQ ID NO:1);

12 X4 is selected from the group consisting of S, T, Y, D, E, hydroxylysine,  
 13 hydroxyproline, phosphoserine analogs and phosphotyrosine analogs;  
 14 X5 is 0, 1, 2, or 3 amino acids of a sequence of genus Z1-Z2-Z3,  
 15 wherein Z1 is selected from the group consisting of G and D;  
 16 Z2 is selected from the group consisting of L and K; and  
 17 Z3 is selected from the group consisting of S, T, and K;  
 18 X6 is absent or comprises a transduction domain; and  
 19 wherein u is 1-5; and

20 (b) general formula II:  
 21 J1-J2-[J3-A(J4)APLP-J5]<sub>u</sub>-J6  
 22 wherein J1 is absent or is one or more molecules comprising one or more  
 23 aromatic ring;  
 24 J2 is absent or comprises a cell transduction domain;  
 25 J3 is 0-14 amino acids of the sequence of heat shock protein 20 between  
 26 residues 1 and 14 of **SEQ ID NO:298**;  
 27 J4 is selected from the group consisting of S, T, Y, D, E, hydroxylysine,  
 28 hydroxyproline, phosphoserine analogs and phosphotyrosine analogs;  
 29 J5 is 0-140 amino acids of heat shock protein 20 between residues 21 and 160  
 30 of **SEQ ID NO:298**; and  
 31 J6 is absent or comprises a cell transduction domain.

1 11. The method of claim 10 wherein the one or more polypeptides comprise a  
 2 sequence according to general formula I.

1 12. The method of claim 10 wherein the one or more polypeptides comprise a  
 2 sequence according to general formula II.

1 13. The method of claim 10 wherein the one or more polypeptides consists of a  
 2 sequence according to general formula I.

1 14. The method of claim 10 wherein the one or more polypeptides consists of a  
 2 sequence according to general formula II.

1 15. The method of claim 11 wherein at least one of X2 and X6 comprises a  
 2 transduction domain.

- 1 16. The method of claim 12 wherein at least one of J2 and J6 comprises a  
2 transduction domain.
- 1 17. The method of any one of claims 10-16 wherein the individual is suffering  
2 from bradyarrhythmia.
- 1 18. The method of any one of claims 10-16 wherein the individual is suffering  
2 from bradycardia.
- 1 19. The method of any one of claims 10-16 wherein the individual is suffering  
2 from congestive heart failure.
- 1 20. The method of any one of claims 10-16 wherein the individual is suffering  
2 from stunned myocardium.
- 1 21. The method of any one of claims 10-16 wherein the individual is suffering  
2 from pulmonary hypertension.
- 1 22. The method of any one of claims 10-16 wherein the individual is suffering  
2 from diastolic dysfunction.
- 1 23. A method for preventing congestive heart failure, comprising administering to  
2 an individual suffering from or who has had one or more of hypertension, anemia,  
3 hyperthyroidism, aortic stenosis, aortic insufficiency, tricuspid insufficiency,  
4 coarctation of the aorta, septal defects, pulmonary stenosis, tetralogy of Fallot;  
5 arrhythmias, myocardial infarction, cardiomyopathy, pulmonary hypertension, chronic  
6 bronchitis, and emphysema an amount effective to prevent congestive heart failure of  
7 one or more polypeptides comprising a sequence according one or more of:
- 8 (a) general formula I:  
9  $X1-X2-[X3-A(X4)APLP-X5]_n-X6$   
10 wherein X1 is absent or is one or more molecules comprising one or more  
11 aromatic ring;  
12 X2 is absent or comprises a transduction domain;  
13 X3 is 0, 1, 2, 3, or 4 amino acids of the sequence WLRR (SEQ ID NO:1);  
14 X4 is selected from the group consisting of S, T, Y, D, E, hydroxylysine,  
15 hydroxyproline, phosphoserine analogs and phosphotyrosine analogs;

16 X5 is 0, 1, 2, or 3 amino acids of a sequence of genus Z1-Z2-Z3,  
 17 wherein Z1 is selected from the group consisting of G and D;  
 18 Z2 is selected from the group consisting of L and K; and  
 19 Z3 is selected from the group consisting of S, T, and K;  
 20 X6 is absent or comprises a transduction domain; and  
 21 wherein u is 1-5; and

22 (b) general formula II:  
 23 J1-J2-[J3-A(J4)APLP-J5]<sub>u</sub>-J6  
 24 wherein J1 is absent or is one or more molecules comprising one or more  
 25 aromatic ring;  
 26 J2 is absent or comprises a cell transduction domain;  
 27 J3 is 0-14 amino acids of the sequence of heat shock protein 20 between  
 28 residues 1 and 14 of SEQ ID NO:298;  
 29 J4 is selected from the group consisting of S, T, Y, D, E, hydroxylysine,  
 30 hydroxyproline, phosphoserine analogs and phosphotyrosine analogs;  
 31 J5 is 0-140 amino acids of heat shock protein 20 between residues 21 and 160  
 32 of SEQ ID NO:298; and  
 33 J6 is absent or comprises a cell transduction domain.

1 24. A method for preventing pulmonary hypertension, comprising administering  
 2 to an individual suffering from one or more of chronic bronchitis, emphysema,  
 3 pulmonary embolism, and intestinal pulmonary fibrosis an amount effective to  
 4 prevent pulmonary hypertension of one or more polypeptides comprising a sequence  
 5 according one or more of:

6 (a) general formula I:  
 7 X1-X2-[X3-A(X4)APLP-X5]<sub>u</sub>-X6  
 8 wherein X1 is absent or is one or more molecules comprising one or more  
 9 aromatic ring;  
 10 X2 is absent or comprises a transduction domain;  
 11 X3 is 0, 1, 2, 3, or 4 amino acids of the sequence WLRR (SEQ ID NO:1);  
 12 X4 is selected from the group consisting of S, T, Y, D, E, hydroxylysine,  
 13 hydroxyproline, phosphoserine analogs and phosphotyrosine analogs;



14 X5 is 0, 1, 2, or 3 amino acids of a sequence of genus Z1-Z2-Z3,  
 15 wherein Z1 is selected from the group consisting of G and D;  
 16 Z2 is selected from the group consisting of L and K; and  
 17 Z3 is selected from the group consisting of S, T, and K;  
 18 X6 is absent or comprises a transduction domain; and  
 19 wherein u is 1-5; and  
 20 (b) general formula II:  
 21 J1-J2-[J3-A(J4)APLP-J5]<sub>u</sub>-J6  
 22 wherein J1 is absent or is one or more molecules comprising one or more  
 23 aromatic ring;  
 24 J2 is absent or comprises a cell transduction domain;  
 25 J3 is 0-14 amino acids of the sequence of heat shock protein 20 between  
 26 residues 1 and 14 of **SEQ ID NO:298**;  
 27 J4 is selected from the group consisting of S, T, Y, D, E, hydroxylysine,  
 28 hydroxyproline, phosphoserine analogs and phosphotyrosine analogs;  
 29 J5 is 0-140 amino acids of heat shock protein 20 between residues 21 and 160  
 30 of **SEQ ID NO:298**; and  
 31 J6 is absent or comprises a cell transduction domain.

1 25. A method for preventing bradyarrhythmia, comprising administering to an  
 2 individual suffering from one or more of coronary heart disease, and atheroma  
 3 formation, and/or that have had a myocardial infarction, an amount effective to  
 4 prevent bradyarrhythmia of one or more polypeptides comprising a sequence according  
 5 one or more of:

6 (a) general formula I:  
 7 X1-X2-[X3-A(X4)APLP-X5]<sub>u</sub>-X6  
 8 wherein X1 is absent or is one or more molecules comprising one or more  
 9 aromatic ring;  
 10 X2 is absent or comprises a transduction domain;  
 11 X3 is 0, 1, 2, 3, or 4 amino acids of the sequence **WLRR (SEQ ID NO:1)**;  
 12 X4 is selected from the group consisting of S, T, Y, D, E, hydroxylysine,  
 13 hydroxyproline, phosphoserine analogs and phosphotyrosine analogs;

14 X5 is 0, 1, 2, or 3 amino acids of a sequence of genus Z1-Z2-Z3,  
 15 wherein Z1 is selected from the group consisting of G and D;  
 16 Z2 is selected from the group consisting of L and K; and  
 17 Z3 is selected from the group consisting of S, T, and K;  
 18 X6 is absent or comprises a transduction domain; and  
 19 wherein u is 1-5; and  
 20 (b) general formula II:  
 21 J1-J2-[J3-A(J4)APLP-J5]<sub>u</sub>-J6  
 22 wherein J1 is absent or is one or more molecules comprising one or more  
 23 aromatic ring;  
 24 J2 is absent or comprises a cell transduction domain;  
 25 J3 is 0-14 amino acids of the sequence of heat shock protein 20 between  
 26 residues 1 and 14 of SEQ ID NO:298;  
 27 J4 is selected from the group consisting of S, T, Y, D, E, hydroxylysine,  
 28 hydroxyproline, phosphoserine analogs and phosphotyrosine analogs;  
 29 J5 is 0-140 amino acids of heat shock protein 20 between residues 21 and 160  
 30 of SEQ ID NO:298; and  
 31 J6 is absent or comprises a cell transduction domain.

1 26. A method for preventing stunned myocardium, comprising administering to an  
 2 individual suffering from cardiac ischemia an amount effective to prevent stunned  
 3 myocardium of one or more polypeptides comprising a sequence according one or  
 4 more of:

5 (a) general formula I:  
 6 X1-X2-[X3-A(X4)APLP-X5]<sub>u</sub>-X6  
 7 wherein X1 is absent or is one or more molecules comprising one or more  
 8 aromatic ring;  
 9 X2 is absent or comprises a transduction domain;  
 10 X3 is 0, 1, 2, 3, or 4 amino acids of the sequence WLRR (SEQ ID NO:1);  
 11 X4 is selected from the group consisting of S, T, Y, D, E, hydroxylysine,  
 12 hydroxyproline, phosphoserine analogs and phosphotyrosine analogs;  
 13 X5 is 0, 1, 2, or 3 amino acids of a sequence of genus Z1-Z2-Z3,  
 14 wherein Z1 is selected from the group consisting of G and D;

15 Z2 is selected from the group consisting of L and K; and  
 16 Z3 is selected from the group consisting of S, T, and K;  
 17 X6 is absent or comprises a transduction domain; and  
 18 wherein u is 1-5; and  
 19 (b) general formula II:  
 20 J1-J2-[J3-A(J4)APLP-J5]<sub>u</sub>-J6  
 21 wherein J1 is absent or is one or more molecules comprising one or more  
 22 aromatic ring;  
 23 J2 is absent or comprises a cell transduction domain;  
 24 J3 is 0-14 amino acids of the sequence of heat shock protein 20 between  
 25 residues 1 and 14 of **SEQ ID NO:298**;  
 26 J4 is selected from the group consisting of S, T, Y, D, E, hydroxylysine,  
 27 hydroxyproline, phosphoserine analogs and phosphotyrosine analogs;  
 28 J5 is 0-140 amino acids of heat shock protein 20 between residues 21 and 160  
 29 of **SEQ ID NO:298**; and  
 30 J6 is absent or comprises a cell transduction domain.

1 27. A method for preventing diastolic dysfunction, comprising administering to an  
 2 individual suffering from left ventricular hypertrophy an amount effective to prevent  
 3 diastolic dysfunction of one or more polypeptides comprising a sequence according  
 4 one or more of:

5 (a) general formula I:  
 6 X1-X2-[X3-A(X4)APLP-X5]<sub>u</sub>-X6  
 7 wherein X1 is absent or is one or more molecules comprising one or more  
 8 aromatic ring;  
 9 X2 is absent or comprises a transduction domain;  
 10 X3 is 0, 1, 2, 3, or 4 amino acids of the sequence **WLRR (SEQ ID NO:1)**;  
 11 X4 is selected from the group consisting of S, T, Y, D, E, hydroxylysine,  
 12 hydroxyproline, phosphoserine analogs and phosphotyrosine analogs;  
 13 X5 is 0, 1, 2, or 3 amino acids of a sequence of genus Z1-Z2-Z3,  
 14 wherein Z1 is selected from the group consisting of G and D;  
 15 Z2 is selected from the group consisting of L and K; and  
 16 Z3 is selected from the group consisting of S, T, and K;

17 X6 is absent or comprises a transduction domain; and

18 wherein u is 1-5; and

19 (b) general formula II:

20 J1-J2-[J3-A(J4)APLP-J5]<sub>u</sub>-J6

21 wherein J1 is absent or is one or more molecules comprising one or more  
22 aromatic ring;

23 J2 is absent or comprises a cell transduction domain;

24 J3 is 0-14 amino acids of the sequence of heat shock protein 20 between  
25 residues 1 and 14 of SEQ ID NO:298;

26 J4 is selected from the group consisting of S, T, Y, D, E, hydroxylysine,  
27 hydroxyproline, phosphoserine analogs and phosphotyrosine analogs;

28 J5 is 0-140 amino acids of heat shock protein 20 between residues 21 and 160  
29 of SEQ ID NO:298; and

30 J6 is absent or comprises a cell transduction domain.

1 28. The method of any one of claims 23-27 wherein the one or more polypeptides  
2 comprise a sequence according to general formula I.

1 29. The method of any one of claims 23-27 wherein the one or more polypeptides  
2 comprise a sequence according to general formula II.

1 30. The method of any one of claims 23-27 wherein the one or more polypeptides  
2 consists of a sequence according to general formula I.

1 31. The method of claim 23-27 wherein the one or more polypeptides consists of a  
2 sequence according to general formula II.

1 32. The method of claim 28 wherein at least one of X2 and X6 comprises a  
2 transduction domain.

1 33. The method of claim 29 wherein at least one of J2 and J6 comprises a  
2 transduction domain.

03-227-PCT seq listing.ST25.txt  
SEQUENCE LISTING

<110> Brophy, C.  
Komalavilas, P.  
Pipkin, W.

<120> Bioactive Peptides for Modulation of Contraction in Heart Muscle

<130> Attorney Docket No. 9138-0130

<140> To Be Assigned  
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<151> 2002-08-22

<150> US 60/448,953  
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<210> 6  
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<210> 7  
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&lt;210&gt; 9

&lt;211&gt; 8

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 9

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1 5

&lt;210&gt; 10

&lt;211&gt; 9

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 10

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1 5

&lt;210&gt; 11

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 11

Trp Leu Arg Arg Ala Ser Ala Pro Leu Pro  
1 5 10

&lt;210&gt; 12

&lt;211&gt; 8

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 12

Arg Arg Ala Thr Ala Pro Leu Pro  
1 5

&lt;210&gt; 13

&lt;211&gt; 9

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

03-227-PCT seq listing.ST25.txt

&lt;223&gt; Description of artificial sequence: artificial peptide

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&lt;210&gt; 14

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 14

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1 5 10

&lt;210&gt; 15

&lt;211&gt; 8

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

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&lt;210&gt; 16

&lt;211&gt; 9

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

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1 5

&lt;210&gt; 17

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 17

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1 5 10

&lt;210&gt; 18

&lt;211&gt; 9

&lt;212&gt; PRT

&lt;213&gt; Artificial



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&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

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&lt;210&gt; 19

&lt;211&gt; 9

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

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Arg Arg Ala Ser Ala Pro Leu Pro Asp  
1 5

&lt;210&gt; 20

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

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&lt;210&gt; 21

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

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1 5 10

&lt;210&gt; 22

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 22

Arg Arg Ala Ser Ala Pro Leu Pro Asp Leu  
1 5 10

&lt;210&gt; 23

&lt;211&gt; 10

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<220>  
<223> Description of artificial sequence: artificial peptide

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<210> 24  
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<210> 27  
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1 5 10

<210> 30  
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<212> PRT  
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1 5 10

<210> 31  
<211> 11  
<212> PRT  
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<220>  
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1 5 10

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1 5 10

<210> 36  
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<210> 37  
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<400> 37

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<210> 39  
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<210> 41  
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<210> 42  
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<220>  
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&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 43

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1 5 10

&lt;210&gt; 44

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 44

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&lt;210&gt; 45

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 45

Leu Arg Arg Ala Ser Ala Pro Leu Pro Asp Lys Thr  
1 5 10

&lt;210&gt; 46

&lt;211&gt; 11

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 46

Trp Leu Arg Arg Ala Ser Ala Pro Leu Pro Gly  
1 5 10

&lt;210&gt; 47

&lt;211&gt; 11

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

03-227-PCT seq listing.ST25.txt

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 47

Trp Leu Arg Arg Ala Ser Ala Pro Leu Pro Asp  
1 5 10

&lt;210&gt; 48

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 48

Trp Leu Arg Arg Ala Ser Ala Pro Leu Pro Gly Leu  
1 5 10

&lt;210&gt; 49

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 49

Trp Leu Arg Arg Ala Ser Ala Pro Leu Pro Gly Lys  
1 5 10

&lt;210&gt; 50

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 50

Trp Leu Arg Arg Ala Ser Ala Pro Leu Pro Asp Leu  
1 5 10

&lt;210&gt; 51

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 51

Trp Leu Arg Arg Ala Ser Ala Pro Leu Pro Asp Lys  
1 5 10

&lt;210&gt; 52

&lt;211&gt; 13

&lt;212&gt; PRT

&lt;213&gt; Artificial

## 03-227-PCT seq listing.ST25.txt

<220>  
<223> Description of artificial sequence: artificial peptide  
<400> 52

Trp Leu Arg Arg Ala Ser Ala Pro Leu Pro Gly Leu Ser  
1 5 10

<210> 53  
<211> 13  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide  
<400> 53

Trp Leu Arg Arg Ala Ser Ala Pro Leu Pro Gly Leu Thr  
1 5 10

<210> 54  
<211> 13  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide  
<400> 54

Trp Leu Arg Arg Ala Ser Ala Pro Leu Pro Gly Lys Ser  
1 5 10

<210> 55  
<211> 13  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide  
<400> 55

Trp Leu Arg Arg Ala Ser Ala Pro Leu Pro Gly Lys Thr  
1 5 10

<210> 56  
<211> 13  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide  
<400> 56

Trp Leu Arg Arg Ala Ser Ala Pro Leu Pro Asp Leu Ser  
1 5 10

<210> 57  
<211> 13



## 03-227-PCT seq listing.ST25.txt

<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide  
<400> 57

Trp Leu Arg Arg Ala Ser Ala Pro Leu Pro Asp Leu Thr  
1 5 10

<210> 58  
<211> 13  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide  
<400> 58

Trp Leu Arg Arg Ala Ser Ala Pro Leu Pro Asp Lys Ser  
1 5 10

<210> 59  
<211> 13  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide  
<400> 59

Trp Leu Arg Arg Ala Ser Ala Pro Leu Pro Asp Lys Thr  
1 5 10

<210> 60  
<211> 9  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide  
<400> 60

Arg Arg Ala Thr Ala Pro Leu Pro Gly  
1 5

<210> 61  
<211> 9  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide  
<400> 61

Arg Arg Ala Thr Ala Pro Leu Pro Asp  
1 5

## 03-227-PCT seq listing.ST25.txt

<210> 62  
<211> 10  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide

<400> 62

Arg Arg Ala Thr Ala Pro Leu Pro Gly Leu  
1 5 10

<210> 63  
<211> 10  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide

<400> 63

Arg Arg Ala Thr Ala Pro Leu Pro Gly Lys  
1 5 10

<210> 64  
<211> 10  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide

<400> 64

Arg Arg Ala Thr Ala Pro Leu Pro Asp Leu  
1 5 10

<210> 65  
<211> 10  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide

<400> 65

Arg Arg Ala Thr Ala Pro Leu Pro Asp Lys  
1 5 10

<210> 66  
<211> 11  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide

<400> 66

Arg Arg Ala Thr Ala Pro Leu Pro Gly Leu Ser  
1 5 10

## 03-227-PCT seq listing.ST25.txt

<210> 67  
<211> 11  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide  
<400> 67

Arg Arg Ala Thr Ala Pro Leu Pro Gly Leu Thr  
1 5 10

<210> 68  
<211> 11  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide  
<400> 68

Arg Arg Ala Thr Ala Pro Leu Pro Gly Lys Ser  
1 5 10

<210> 69  
<211> 11  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide  
<400> 69

Arg Arg Ala Thr Ala Pro Leu Pro Gly Lys Thr  
1 5 10

<210> 70  
<211> 11  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide  
<400> 70

Arg Arg Ala Thr Ala Pro Leu Pro Asp Leu Ser  
1 5 10

<210> 71  
<211> 11  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide  
<400> 71

03-227-PCT seq listing.ST25.txt  
 Arg Arg Ala Thr Ala Pro Leu Pro Asp Leu Thr  
 1 5 10

<210> 72  
 <211> 11  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Description of artificial sequence: artificial peptide  
 <400> 72

Arg Arg Ala Thr Ala Pro Leu Pro Asp Lys Ser  
 1 5 10

<210> 73  
 <211> 11  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Description of artificial sequence: artificial peptide  
 <400> 73

Arg Arg Ala Thr Ala Pro Leu Pro Asp Lys Thr  
 1 5 10

<210> 74  
 <211> 10  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Description of artificial sequence: artificial peptide  
 <400> 74

Leu Arg Arg Ala Thr Ala Pro Leu Pro Gly  
 1 5 10

<210> 75  
 <211> 10  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Description of artificial sequence: artificial peptide  
 <400> 75

Leu Arg Arg Ala Thr Ala Pro Leu Pro Asp  
 1 5 10

<210> 76  
 <211> 11  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Description of artificial sequence: artificial peptide

## 03-227-PCT seq listing.ST25.txt

&lt;400&gt; 76

Leu Arg Arg Ala Thr Ala Pro Leu Pro Gly Leu  
1 5 10

&lt;210&gt; 77

&lt;211&gt; 11

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 77

Leu Arg Arg Ala Thr Ala Pro Leu Pro Gly Lys  
1 5 10

&lt;210&gt; 78

&lt;211&gt; 11

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 78

Leu Arg Arg Ala Thr Ala Pro Leu Pro Asp Leu  
1 5 10

&lt;210&gt; 79

&lt;211&gt; 11

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 79

Leu Arg Arg Ala Thr Ala Pro Leu Pro Asp Lys  
1 5 10

&lt;210&gt; 80

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 80

Leu Arg Arg Ala Thr Ala Pro Leu Pro Gly Leu Ser  
1 5 10

&lt;210&gt; 81

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

03-227-PCT seq listing.ST25.txt

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 81

Leu Arg Arg Ala Thr Ala Pro Leu Pro Gly Leu Thr  
1 5 10

&lt;210&gt; 82

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 82

Leu Arg Arg Ala Thr Ala Pro Leu Pro Gly Lys Ser  
1 5 10

&lt;210&gt; 83

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 83

Leu Arg Arg Ala Thr Ala Pro Leu Pro Gly Lys Thr  
1 5 10

&lt;210&gt; 84

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 84

Leu Arg Arg Ala Thr Ala Pro Leu Pro Asp Leu Ser  
1 5 10

&lt;210&gt; 85

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 85

Leu Arg Arg Ala Thr Ala Pro Leu Pro Asp Leu Thr  
1 5 10

&lt;210&gt; 86

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Artificial

## 03-227-PCT seq listing.ST25.txt

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 86

Leu Arg Arg Ala Thr Ala Pro Leu Pro Asp Lys Ser  
 1 5 10

&lt;210&gt; 87

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 87

Leu Arg Arg Ala Thr Ala Pro Leu Pro Asp Lys Thr  
 1 5 10

&lt;210&gt; 88

&lt;211&gt; 11

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 88

Trp Leu Arg Arg Ala Thr Ala Pro Leu Pro Gly  
 1 5 10

&lt;210&gt; 89

&lt;211&gt; 11

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 89

Trp Leu Arg Arg Ala Thr Ala Pro Leu Pro Asp  
 1 5 10

&lt;210&gt; 90

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 90

Trp Leu Arg Arg Ala Thr Ala Pro Leu Pro Gly Leu  
 1 5 10

&lt;210&gt; 91

&lt;211&gt; 12

## 03-227-PCT seq listing.ST25.txt

<212> PRT  
 <213> Artificial

<220>  
 <223> Description of artificial sequence: artificial peptide

<400> 91

Trp Leu Arg Arg Ala Thr Ala Pro Leu Pro Gly Lys  
 1 5 10

<210> 92  
 <211> 12  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Description of artificial sequence: artificial peptide

<400> 92

Trp Leu Arg Arg Ala Thr Ala Pro Leu Pro Asp Leu  
 1 5 10

<210> 93  
 <211> 12  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Description of artificial sequence: artificial peptide

<400> 93

Trp Leu Arg Arg Ala Thr Ala Pro Leu Pro Asp Lys  
 1 5 10

<210> 94  
 <211> 13  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Description of artificial sequence: artificial peptide

<400> 94

Trp Leu Arg Arg Ala Thr Ala Pro Leu Pro Gly Leu Ser  
 1 5 10

<210> 95  
 <211> 13  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Description of artificial sequence: artificial peptide

<400> 95

Trp Leu Arg Arg Ala Thr Ala Pro Leu Pro Gly Leu Thr  
 1 5 10



## 03-227-PCT seq listing.ST25.txt

<210> 96  
<211> 13  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide

<400> 96

Trp Leu Arg Arg Ala Thr Ala Pro Leu Pro Gly Lys Ser  
1 5 10

<210> 97  
<211> 13  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide

<400> 97

Trp Leu Arg Arg Ala Thr Ala Pro Leu Pro Gly Lys Thr  
1 5 10

<210> 98  
<211> 13  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide

<400> 98

Trp Leu Arg Arg Ala Thr Ala Pro Leu Pro Asp Leu Ser  
1 5 10

<210> 99  
<211> 13  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide

<400> 99

Trp Leu Arg Arg Ala Thr Ala Pro Leu Pro Asp Leu Thr  
1 5 10

<210> 100  
<211> 13  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide

<400> 100

Trp Leu Arg Arg Ala Thr Ala Pro Leu Pro Asp Lys Ser  
1 5 10

## 03-227-PCT seq listing.ST25.txt

<210> 101  
<211> 13  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide  
<400> 101

Trp Leu Arg Arg Ala Thr Ala Pro Leu Pro Asp Lys Thr  
1 5 10

<210> 102  
<211> 9  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide  
<400> 102

Arg Arg Ala Tyr Ala Pro Leu Pro Gly  
1 5

<210> 103  
<211> 9  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide  
<400> 103

Arg Arg Ala Tyr Ala Pro Leu Pro Asp  
1 5

<210> 104  
<211> 10  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide  
<400> 104

Arg Arg Ala Tyr Ala Pro Leu Pro Gly Leu  
1 5 10

<210> 105  
<211> 10  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide  
<400> 105

## 03-227-PCT seq listing.ST25.txt

Arg Arg Ala Tyr Ala Pro Leu Pro Gly Lys  
 1 5 10

<210> 106  
 <211> 10  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Description of artificial sequence: artificial peptide  
 <400> 106

Arg Arg Ala Tyr Ala Pro Leu Pro Asp Leu  
 1 5 10

<210> 107  
 <211> 10  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Description of artificial sequence: artificial peptide  
 <400> 107

Arg Arg Ala Tyr Ala Pro Leu Pro Asp Lys  
 1 5 10

<210> 108  
 <211> 11  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Description of artificial sequence: artificial peptide  
 <400> 108

Arg Arg Ala Tyr Ala Pro Leu Pro Gly Leu Ser  
 1 5 10

<210> 109  
 <211> 11  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Description of artificial sequence: artificial peptide  
 <400> 109

Arg Arg Ala Tyr Ala Pro Leu Pro Gly Leu Thr  
 1 5 10

<210> 110  
 <211> 11  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Description of artificial sequence: artificial peptide

## 03-227-PCT seq listing.ST25.txt

&lt;400&gt; 110

Arg Arg Ala Tyr Ala Pro Leu Pro Gly Lys Ser  
1 5 10

&lt;210&gt; 111

&lt;211&gt; 11

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 111

Arg Arg Ala Tyr Ala Pro Leu Pro Gly Lys Thr  
1 5 10

&lt;210&gt; 112

&lt;211&gt; 11

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 112

Arg Arg Ala Tyr Ala Pro Leu Pro Asp Leu Ser  
1 5 10

&lt;210&gt; 113

&lt;211&gt; 11

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 113

Arg Arg Ala Tyr Ala Pro Leu Pro Asp Leu Thr  
1 5 10

&lt;210&gt; 114

&lt;211&gt; 11

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 114

Arg Arg Ala Tyr Ala Pro Leu Pro Asp Lys Ser  
1 5 10

&lt;210&gt; 115

&lt;211&gt; 11

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

03-227-PCT seq listing.ST25.txt

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 115

Arg Arg Ala Tyr Ala Pro Leu Pro Asp Lys Thr  
 1 5 10

&lt;210&gt; 116

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 116

Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly  
 1 5 10

&lt;210&gt; 117

&lt;211&gt; 10

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 117

Leu Arg Arg Ala Tyr Ala Pro Leu Pro Asp  
 1 5 10

&lt;210&gt; 118

&lt;211&gt; 11

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 118

Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly Leu  
 1 5 10

&lt;210&gt; 119

&lt;211&gt; 11

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 119

Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly Lys  
 1 5 10

&lt;210&gt; 120

&lt;211&gt; 11

&lt;212&gt; PRT

&lt;213&gt; Artificial

## 03-227-PCT seq listing.ST25.txt

<220>  
 <223> Description of artificial sequence: artificial peptide  
 <400> 120  
 Leu Arg Arg Ala Tyr Ala Pro Leu Pro Asp Leu  
 1 5 10

<210> 121  
 <211> 11  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Description of artificial sequence: artificial peptide  
 <400> 121

Leu Arg Arg Ala Tyr Ala Pro Leu Pro Asp Lys  
 1 5 10

<210> 122  
 <211> 12  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Description of artificial sequence: artificial peptide  
 <400> 122

Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly Leu Ser  
 1 5 10

<210> 123  
 <211> 12  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Description of artificial sequence: artificial peptide  
 <400> 123

Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly Leu Thr  
 1 5 10

<210> 124  
 <211> 12  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Description of artificial sequence: artificial peptide  
 <400> 124

Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly Lys Ser  
 1 5 10

<210> 125  
 <211> 12

## 03-227-PCT seq listing.ST25.txt

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 125

Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly Lys Thr  
1 5 10

&lt;210&gt; 126

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 126

Leu Arg Arg Ala Tyr Ala Pro Leu Pro Asp Leu Ser  
1 5 10

&lt;210&gt; 127

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 127

Leu Arg Arg Ala Tyr Ala Pro Leu Pro Asp Leu Thr  
1 5 10

&lt;210&gt; 128

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 128

Leu Arg Arg Ala Tyr Ala Pro Leu Pro Asp Lys Ser  
1 5 10

&lt;210&gt; 129

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 129

Leu Arg Arg Ala Tyr Ala Pro Leu Pro Asp Lys Thr  
1 5 10

## 03-227-PCT seq listing.ST25.txt

&lt;210&gt; 130

&lt;211&gt; 11

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 130

Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly  
1 5 10

&lt;210&gt; 131

&lt;211&gt; 11

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 131

Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Asp  
1 5 10

&lt;210&gt; 132

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 132

Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly Leu  
1 5 10

&lt;210&gt; 133

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 133

Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly Lys  
1 5 10

&lt;210&gt; 134

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 134

Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Asp Leu  
1 5 10



## 03-227-PCT seq listing.ST25.txt

<210> 135  
<211> 12  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide  
<400> 135

Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Asp Lys  
1 5 10

<210> 136  
<211> 13  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide  
<400> 136

Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly Leu Ser  
1 5 10

<210> 137  
<211> 13  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide  
<400> 137

Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly Leu Thr  
1 5 10

<210> 138  
<211> 13  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide  
<400> 138

Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly Lys Ser  
1 5 10

<210> 139  
<211> 13  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide  
<400> 139

## 03-227-PCT seq listing.ST25.txt

Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly Lys Thr  
1 5 10

<210> 140  
<211> 13  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide

<400> 140

Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Asp Leu Ser  
1 5 10

<210> 141  
<211> 13  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide

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&lt;400&gt; 144

Xaa Arg Arg Ala Ser Ala Pro Leu Pro

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&lt;210&gt; 241

&lt;211&gt; 11

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&lt;213&gt; Artificial

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<223> Description of artificial sequence: artificial peptide

<220>  
<221> MISC\_FEATURE  
<222> (1)..(1)  
<223> Xaa is Phe, Tyr, or Trp

<400> 264

Xaa Leu Arg Arg Ala Tyr Ala Pro Leu Pro Asp Lys Thr  
1 5 10

<210> 265  
<211> 12  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide

<220>  
<221> MISC\_FEATURE  
<222> (1)..(1)  
<223> Xaa is Phe, Tyr, or Trp

<400> 265

Xaa Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly  
1 5 10

<210> 266  
<211> 12  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide

<220>  
<221> MISC\_FEATURE  
<222> (1)..(1)  
<223> Xaa is Phe, Tyr, or Trp

<400> 266

## 03-227-PCT seq listing.ST25.txt

Xaa Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Asp  
1 5 10

<210> 267  
<211> 13  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide

<220>  
<221> MISC\_FEATURE  
<222> (1)..(1)  
<223> Xaa is Phe, Tyr, or Trp

<400> 267

Xaa Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly Leu  
1 5 10

<210> 268  
<211> 13  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide

<220>  
<221> MISC\_FEATURE  
<222> (1)..(1)  
<223> Xaa is Phe, Tyr, or Trp

<400> 268

Xaa Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly Lys  
1 5 10

<210> 269  
<211> 13  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide

<220>  
<221> MISC\_FEATURE  
<222> (1)..(1)  
<223> Xaa is Phe, Tyr, or Trp

<400> 269

Xaa Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Asp Leu  
1 5 10

<210> 270  
<211> 13  
<212> PRT  
<213> Artificial

## 03-227-PCT seq listing.ST25.txt

<220>  
<223> Description of artificial sequence: artificial peptide

<220>  
<221> MISC\_FEATURE  
<222> (1)..(1)  
<223> Xaa is Phe, Tyr, or Trp

<400> 270

Xaa Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Asp Lys  
1 5 10

<210> 271  
<211> 14  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide

<220>  
<221> MISC\_FEATURE  
<222> (1)..(1)  
<223> Xaa is Phe, Tyr, or Trp

<400> 271

Xaa Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly Leu Ser  
1 5 10

<210> 272  
<211> 14  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide

<220>  
<221> MISC\_FEATURE  
<222> (1)..(1)  
<223> Xaa is Phe, Tyr, or Trp

<400> 272

Xaa Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly Leu Thr  
1 5 10

<210> 273  
<211> 14  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide

<220>  
<221> MISC\_FEATURE  
<222> (1)..(1)



03-227-PCT seq listing.ST25.txt  
<223> Xaa is Phe, Tyr, or Trp

<400> 273

Xaa Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly Lys Ser  
1 5 10

<210> 274

<211> 14

<212> PRT

<213> Artificial

<220>

<223> Description of artificial sequence: artificial peptide

<220>

<221> MISC\_FEATURE

<222> (1)..(1)

<223> Xaa is Phe, Tyr, or Trp

<400> 274

Xaa Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Gly Lys Thr  
1 5 10

<210> 275

<211> 14

<212> PRT

<213> Artificial

<220>

<223> Description of artificial sequence: artificial peptide

<220>

<221> MISC\_FEATURE

<222> (1)..(1)

<223> Xaa is Phe, Tyr, or Trp

<400> 275

Xaa Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Asp Leu Ser  
1 5 10

<210> 276

<211> 14

<212> PRT

<213> Artificial

<220>

<223> Description of artificial sequence: artificial peptide

<220>

<221> MISC\_FEATURE

<222> (1)..(1)

<223> Xaa is Phe, Tyr, or Trp

<400> 276

Xaa Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Asp Leu Thr  
1 5 10

## 03-227-PCT seq listing.ST25.txt

<210> 277  
<211> 14  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide

<220>  
<221> MISC\_FEATURE  
<222> (1)..(1)  
<223> Xaa is Phe, Tyr, or Trp

<400> 277

Xaa Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Asp Lys Ser  
1 5 10

<210> 278  
<211> 14  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide

<220>  
<221> MISC\_FEATURE  
<222> (1)..(1)  
<223> Xaa is Phe, Tyr, or Trp

<400> 278

Xaa Trp Leu Arg Arg Ala Tyr Ala Pro Leu Pro Asp Lys Thr  
1 5 10

<210> 279  
<211> 1  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide

<220>  
<221> MISC\_FEATURE  
<222> (1)..(1)  
<223> Xaa is (Arg)4-9

<400> 279

Xaa  
1

<210> 280  
<211> 13  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide

## 03-227-PCT seq listing.ST25.txt

&lt;400&gt; 280

Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg Pro Pro Gln  
1 5 10

&lt;210&gt; 281

&lt;211&gt; 11

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 281

Tyr Ala Arg Ala Ala Ala Arg Gln Ala Arg Ala  
1 5 10

&lt;210&gt; 282

&lt;211&gt; 34

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 282

Asp Ala Ala Thr Ala Thr Arg Gly Arg Ser Ala Ala Ser Arg Pro Thr  
1 5 10 15

Glu Arg Pro Arg Ala Pro Ala Arg Ser Ala Ser Arg Pro Arg Arg Pro  
20 25 30

Val Glu

&lt;210&gt; 283

&lt;211&gt; 27

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 283

Gly Trp Thr Leu Asn Ser Ala Gly Tyr Leu Leu Gly Leu Ile Asn Leu  
1 5 10 15

Lys Ala Leu Ala Ala Leu Ala Lys Lys Ile Leu  
20 25

&lt;210&gt; 284

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

## 03-227-PCT seq listing.ST25.txt

&lt;400&gt; 284

Pro Leu Ser Ser Ile Phe Ser Arg Ile Gly Asp Pro  
 1 5 10

&lt;210&gt; 285

&lt;211&gt; 16

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 285

Ala Ala Val Ala Leu Leu Pro Ala Val Leu Leu Ala Leu Leu Ala Pro  
 1 5 10 15

&lt;210&gt; 286

&lt;211&gt; 12

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 286

Ala Ala Val Leu Leu Pro Val Leu Leu Ala Ala Pro  
 1 5 10

&lt;210&gt; 287

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 287

Val Thr Val Leu Ala Leu Gly Ala Leu Ala Gly Val Gly Val Gly  
 1 5 10 15

&lt;210&gt; 288

&lt;211&gt; 21

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 288

Gly Ala Leu Phe Leu Gly Trp Leu Gly Ala Ala Gly Ser Thr Met Gly  
 1 5 10 15

Ala Trp Ser Gln Pro  
 20

&lt;210&gt; 289

&lt;211&gt; 27

## 03-227-PCT seq listing.ST25.txt

<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide

<400> 289

Gly Trp Thr Leu Asn Ser Ala Gly Tyr Leu Leu Gly Leu Ile Asn Leu  
1 5 10 15

Lys Ala Leu Ala Ala Leu Ala Lys Lys Ile Leu  
20 25

<210> 290  
<211> 18  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide

<400> 290

Lys Leu Ala Leu Lys Leu Ala Leu Lys Ala Leu Lys Ala Ala Leu Lys  
1 5 10 15

Leu Ala

<210> 291  
<211> 21  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide

<400> 291

Lys Glu Thr Trp Trp Glu Thr Trp Trp Thr Glu Trp Ser Gln Pro Lys  
1 5 10 15

Lys Lys Arg Lys Val  
20

<210> 292  
<211> 16  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: artificial peptide

<400> 292

Lys Ala Phe Ala Lys Leu Ala Ala Arg Leu Tyr Arg Lys Ala Gly Cys  
1 5 10 15

<210> 293  
<211> 16

## 03-227-PCT seq listing.ST25.txt

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 293

Lys Ala Phe Ala Lys Leu Ala Ala Arg Leu Tyr Arg Ala Ala Gly Cys  
 1 5 10 15

&lt;210&gt; 294

&lt;211&gt; 16

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 294

Ala Ala Phe Ala Lys Leu Ala Ala Arg Leu Tyr Arg Lys Ala Gly Cys  
 1 5 10 15

&lt;210&gt; 295

&lt;211&gt; 16

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 295

Lys Ala Phe Ala Ala Leu Ala Ala Arg Leu Tyr Arg Lys Ala Gly Cys  
 1 5 10 15

&lt;210&gt; 296

&lt;211&gt; 16

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 296

Lys Ala Phe Ala Lys Leu Ala Ala Gln Leu Tyr Arg Lys Ala Gly Cys  
 1 5 10 15

&lt;210&gt; 297

&lt;211&gt; 15

&lt;212&gt; PRT

&lt;213&gt; Artificial

&lt;220&gt;

&lt;223&gt; Description of artificial sequence: artificial peptide

&lt;400&gt; 297

Gly Gly Gly Gly Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg  
 1 5 10 15

## 03-227-PCT seq listing.ST25.txt

<210> 298  
 <211> 160  
 <212> PRT  
 <213> Homo sapiens

<400> 298

Met Glu Ile Pro Val Pro Val Gln Pro Ser Trp Leu Arg Arg Ala Ser  
 1 5 10 15

Ala Pro Leu Pro Gly Leu Ser Ala Pro Gly Arg Leu Phe Asp Gln Arg  
 20 25 30

Phe Gly Glu Gly Leu Leu Glu Ala Glu Leu Ala Ala Leu Cys Pro Thr  
 35 40 45

Thr Leu Ala Pro Tyr Tyr Leu Arg Ala Pro Ser Val Ala Leu Pro Val  
 50 55 60

Ala Gln Val Pro Thr Asp Pro Gly His Phe Ser Val Leu Leu Asp Val  
 65 70 75 80

Lys His Phe Ser Pro Glu Glu Ile Ala Val Lys Val Val Gly Glu His  
 85 90 95

Val Glu Val His Ala Arg His Glu Glu Arg Pro Asp Glu His Gly Phe  
 100 105 110

Val Ala Arg Glu Phe His Arg Arg Tyr Arg Leu Pro Pro Gly Val Asp  
 115 120 125

Pro Ala Ala Val Thr Ser Ala Leu Ser Pro Glu Gly Val Leu Ser Ile  
 130 135 140

Gln Ala Ala Pro Ala Ser Ala Gln Ala Pro Pro Pro Ala Ala Ala Lys  
 145 150 155 160

<210> 299  
 <211> 13  
 <212> PRT  
 <213> Artificial

<220>  
 <223> Description of artificial sequence: a scrambled phosphorylated peptide

<220>  
 <221> MOD\_RES  
 <222> (4)..(4)  
 <223> Phosphorylated Ser

<400> 299

Pro Arg Lys Ser Leu Trp Ala Leu Gly Arg Pro Leu Ala  
 1 5 10

## 03-227-PCT seq listing.ST25.txt

<210> 300  
<211> 13  
<212> PRT  
<213> Artificial

<220>  
<223> Description of artificial sequence: phospho HSP20 peptide  
analogue

<220>  
<221> MOD\_RES  
<222> (6)..(6)  
<223> Phosphorylated ser

<400> 300

Trp Leu Arg Arg Ala Ser Ala Pro Leu Pro Gly Leu Lys  
1 5 10